# INTERNATIONAL HEALTH NEWS

*Your Gateway to Better Health!*

**NUMBER 139** **JULY/AUGUST 2003** **12th YEAR**

*Welcome to our blockbuster combined July/August issue. This month we begin a new series of articles by Professor William Ware. This time Dr. Ware provides an in-depth look at Alzheimer's disease, its probable causes, prevention and treatment. It is a must read for everyone. Although symptoms of Alzheimer's usually only become apparent fairly late in life, prevention, to be effective, should begin as early as possible.*

*With this being our summer issue we also include an article by Thomas Ogren on garden design, stress and allergies. Thomas is an internationally recognized expert on plant sexuality as it relates to human health. His article is a delightful read, full of wisdom and suggestions for alleviating stress and enjoying your garden to its fullest.*

*And of course, there is our usual round-up of the latest health news – the use of diet and antioxidants to prevent glaucoma, the benefits of fish oils, DHEA and almonds, an exciting new test for prostate cancer, and a warning concerning MRI scans and pacemakers.*

*Enjoy and have a great summer!*

*Yours in health,*
*Hans Larsen, Editor*

**July/August Highlights**



## Paleolithic diet and alpha-lipoic acid for glaucoma

TUCSON, ARIZONA. It is estimated that about 3 million Americans are affected by glaucoma, the second leading cause of blindness (after macular degeneration). The main risk factor for glaucoma is an elevation of intraocular eye pressure (IOP) with an IOP of greater than 21 mm Hg being considered indicative of a future risk of glaucoma. Chronically elevated glucose levels, such as found in diabetics, increase the risk of not only glaucoma, but also of cataracts and age-related macular degeneration. There is now evidence that adhering to a Paleolithic diet (lean meat, fish, non-starchy vegetables and nuts with little or no grains, dairy products and potatoes – or other high glycemic index vegetables) can reduce the risk of diabetes and its precursor, Syndrome X. There is also evidence that alpha-lipoic acid, a powerful antioxidant, can reduce glucose levels by facilitating uptake and sensitizing insulin.

Jack Challem, a medical editor in Arizona reports two cases where patients diagnosed with IOPs over 21 mm Hg were able to lower their IOPs to normal levels by switching to a Paleolithic diet and/or supplementing with alpha-lipoic acid. The first patient, a 45-year-old man, switched to a Paleolithic diet and began taking 380 mg/day of alpha-lipoic acid as well as several other

supplements (magnesium citrate, chromium, vitamin E, vitamin C). In September 1997 his fasting glucose level was 111 mg/dL. By November 1999 this had been reduced to 85 mg/dL and by September 2000 his IOP was 16 mm Hg in both eyes.

The other patient with elevated IOP, an 84-year-old man, began supplementing with alpha-lipoic acid (200 mg 3 times daily after meals) and in less than a year had reduced his IOP to 20 in both eyes. Although anecdotal evidence only, these observations point to the possibility that following a Paleolithic diet and supplementing with alpha-lipoic acid may be helpful in warding off not only glaucoma and other eye diseases, but diabetes as well.

*Challem, Jack J. Natural therapies for reducing intraocular eye pressure: Rationale and two case reports*. **Journal of Orthomolecular Medicine**, *Vol. 17, No. 4, 4th quarter, 2002, pp. 209-12*

## Fish oils benefit women with diabetes

BOSTON, MASSACHUSETTS. Several studies have found a clear inverse association between the consumption of fish and fish oils and the risk of coronary heart disease (CHD) and sudden cardiac death. However, it is not known whether this protective effect extends to diabetes patients. Researchers at the Harvard Medical School have just concluded a study to examine this. Their study included 5103 female nurses with diabetes, but free of cardiovascular disease and cancer at entry. Between 1980 and 1996 there were 362 cases of CHD (7.1%) and 468 deaths from all causes in the study group (9.2%). The causes of death were CHD or stroke – 161, cancer – 172, and other causes – 135.

Study participants completed detailed food frequency questionnaires in 1980, 1984, 1986, 1990 and 1994. The researchers noted a strong correlation between the risk of CHD and fish intake. Women who consumed fish once a week had a 40% lower risk of CHD than did women who consumed fish less than once per month. Eating fish 5 times per week reduced CHD risk by 64% and overall mortality by 52%. Only dark-meat fish (mackerel, salmon, sardines, bluefish, and swordfish) and shrimp, lobster and scallops showed a beneficial effect. The researchers also calculated the amount of fish oils (eicosapentaenoic acid and docosahexaenoic acid) obtained from the diet and found that study participants with an average intake of just 250 mg/day had a 31% reduction in CHD and a 37% reduction in death from all causes compared to participants with a low (40 mg or less) daily intake. The researchers note that fish oil supplementation does not impair glycemic control and suggest that regular fish consumption should be considered as an integral part of a healthy diet for the management of diabetes.

*Hu, Frank B., et al. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women*. **Circulation,** *Vol. 107, April 15, 2003, pp. 1852-57*

*Grundy, Scott M. N-3 fatty acids: priority for post-myocardial infarction clinical trials*. **Circulation**, *Vol. 107, April 15, 2003, pp. 1834-36 (editorial)*

**Editor's comment**: Swordfish, bluefish and king mackerel have high levels of mercury or methyl mercury and should not be eaten regularly, if at all.

## DHEA helps alleviate schizophrenia symptoms

BEER YAAKOV, ISRAEL. The main symptoms of schizophrenia are delusions and hallucination and these can often be managed with antipsychotic medication. However, schizophrenics also tend to be anxious and depressed, lacking in motivation and initiative to pursue a goal, and to suffer from the absence of pleasure from the performance of acts that would normally be pleasurable. These other negative symptoms are much more difficult to treat. Researchers at the Beer Yaakov Mental Health Center now report that daily supplementation with the steroid hormone dehydroepiandrosterone (DHEA) can markedly reduce anxiety, depression and other negative symptoms.

Their clinical trial involved 27 schizophrenics between the ages of 20 and 67 years (15 men and 12 women). The patients were randomized to receive either DHEA daily or a placebo for the

6-week trial period. The starting dose (first 2 weeks) was 25 mg/day (taken at 8 am); this was followed by 2 x 25 mg/day (taken at 8 am and 8 pm) for the next 2 weeks, and then 2 x 50 mg/day (taken at 8 am and 8 pm) for the remainder of the trial. This regimen brought circulating DHEA and DHEAS levels to the range found in health 20- to 30-year-olds.

The researchers noted a marked decrease in anxiety, depression and other negative symptoms among the DHEA-treated patients and conclude that DHEA supplementation may be useful in alleviating these symptoms in schizophrenia patients although, clearly, larger trials are required to confirm this.

*Strous, Rael D., et al. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia*. **Archives of General Psychiatry**, *Vol. 60, February 2003, pp. 133-41*

## Congestive heart failure and homocysteine

FRAMINGHAM, MASSACHUSETTS. Congestive heart failure (CHF) is a serious health problem among the elderly. The main risk factors are advancing age, high blood pressure (hypertension), diabetes, obesity, heart valve disease, and having experienced a heart attack. Researchers involved with the Framingham Heart Study now report that a high blood level of homocysteine, a sulfur-containing amino acid, is an independent risk factor for CHF. Their study involved 1547 women and 944 men between the ages of 60 and 95 years. All participants were free of CHF and had not suffered a heart attack at the start of the study. After 8 years of follow-up 156 (6.2%) participants (88 women) had developed CHF. The researchers found that women in the highest quartile of homocysteine level (13.7 – 64.6 micromol/L) had a 4 times higher risk of CHF than did those in the lowest quartile (3.5 – 8.9 micromol/L). Even women with only slightly elevated homocysteine levels (9.0 – 11.0) had twice the risk of women in the lowest quartile. The risk for men in the highest quartile (14.5 – 219.8 micromol/L) was 50% higher than for men in the lowest quartile (4.1 – 9.5 micromol/L); however, a significant increase was not observed until the level exceeded 11.8 micromol/L. The risk estimates are those obtained after adjusting for age, smoking, valve disease, systolic blood pressure, antihypertensive medication use, echocardiographic left ventricular hypertrophy, diabetes, ratio of total cholesterol to high-density lipoprotein, alcohol intake, body mass index, serum creatinine, interim recognized or unrecognized myocardial infarction, and baseline examination.

The researchers urge further trials to determine if reducing elevated homocysteine levels through supplementation with folic acid, vitamin B6 and vitamins B12 will reduce the risk of CHF.

*Vasan, Ramachandran S., et al. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction*. **Journal of the American Medical Association**, *Vol. 289, March 12, 2003, pp. 1251-57*

**Editor's comment**: Homocysteine levels can be safely and effectively lowered by daily supplementation with 400-800 micrograms of folic acid, 50-100 mg of vitamin B6 (pyridoxine) and 1 mg of vitamin B12 (cyanocobalamin) taken sublingually.

## Almonds reduce cholesterol levels

LOMA LINDA, CALIFORNIA. Researchers at Loma Linda University report that the addition of almonds to the diet results in a significant reduction in cholesterol levels. Their clinical trial involved 25 healthy subjects (14 men, 11 women) aged 22 to 53 years. The participants consumed 3 different diets in 3 separate 4-week periods. Diet 1 was patterned on the National Cholesterol Education Program (NCEP) Step 1 diet; diet 2 was the NCEP diet with 10% of energy (34 grams) contributed by almonds, and diet 3 with 20% of energy contributed by almonds. The three diets had the same calorie content and the energy contributed by fat was 30%, 35% (low-almond diet) and 39% (high-almond diet) respectively. Blood samples were drawn and analyzed at the beginning and end of each 4-week diet period.

The researchers found that participants on the high-almond diet reduced their overall cholesterol level by 4.4% as compared to the NCEP Step 1 diet. LDL cholesterol and apolipoprotein B were reduced by 7% and 6.6% respectively and the LDL/HDL ratio decreased by 8.8%. The researchers estimate that the 7% reduction in LDL corresponds to an 11% reduction in the risk of heart disease. They point out that almonds contain beneficial mono-unsaturated fats, a high concentration of alpha-tocopherol, and an unusually large amount of arginine, the precursor of nitric oxide. They suggest that daily consumption of as little as 34 grams (a handful – 35 almonds) may be sufficient to produce clinically relevant reductions in cholesterol levels. NOTE: This study was supported by a research grant from the Almond Board of California.

*Sabate, Joan, et al. Serum lipid response to the graduated enrichment of a Step 1 diet with almonds: a randomized feeding trial*. **American Journal of Clinical Nutrition**, *Vol. 77, June 2003, pp. 1379-84*

## Slippers and hip fractures

RANDWICK, NSW, AUSTRALIA. Hip fractures are a serious health problem among older men and women. It is estimated that by age 90 years, as many as 17% of men and 32% of women have suffered a hip fracture. A hip fracture is usually a consequence of a fall and it is estimated that 1 in 3 older people fall at least once a year. Researchers at the Prince of Wales Medical Research Institute now report that the type of footwear worn in the home may be a crucial factor in determining the risk of a fall. Their study involved 95 older people (average age of 78 years) who had suffered a hip fracture as the result of a fall. The researchers found that 22% of the study participants had been wearing slippers when they fell, 17% had been wearing walking shoes, and 8% sandals. The majority of participants (63%) wore shoes with no fixation, that is, no laces, straps, buckles, zippers or Velcro fastenings. Forty-three per cent wore shoes with excessively flexible heel counters, i.e. low-cut or too little support to the back of the heel. Other problems identified involved worn soles with no grip and soles with excessive flexibility. The researchers conclude that the ideal shoe for older people would have a low, sturdy heel, high, non-flexible heel counter, a textured sole and a thin, firm mid-sole.

*Sherrington, Catherine and Menz, Hylton B. An evaluation of footwear worn at the time of fall-related hip fracture*. **Age and Ageing**, *Vol. 32, May 2003, pp. 310-14*

## Aspirin and colon cancer

COPENHAGEN, DENMARK. There is considerable evidence that the use of aspirin in daily doses of 300 mg or more for at least 6 months reduces the risk of colorectal cancer (cancer of the colon or rectum). What is much less clear is whether lower doses of aspirin, such as prescribed for heart disease patients, have a similar protective effect.

Danish medical researchers investigated the incidence of cancer in 15,000 men and 14,000 women (39% between the ages of 50 and 69 years and 55% aged 70 years or older) who had been prescribed a daily low-dose aspirin (75-150 mg) for heart disease. The participants were followed for up to 9 years with an average follow-up period of 4.1 years. During this time, a total of 2381 cases of cancer were diagnosed in the aspirin group. The expected number of cases in a group of 29,000 adults would be 2187. Thus there was no evidence of an overall protective effect of low-dose aspirin. Specifically, there was no indication that long-term use of low-dose aspirin was protective against either cancer of the colon or cancer of the rectum. There was a light, but statistically significant excess of kidney cancer cases among the aspirin users; the researchers ascribe this to a possible greater incidence of hypertension in this group of heart patients and point out that hypertension is a risk factor for kidney cancer.

*Friis, S., et al. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin*. **British Journal of Cancer**, *Vol. 88, March 10, 2003, pp. 684-88*

## New test predicts the risk of prostate cancer

SEATTLE, WASHINGTON. Researchers at the Pacific Northwest Research Institute and Baylor College of Medicine report the development of a promising new method for determining prostate cancer risk and the risk of metastasis. The researchers compared the DNA spectra (Fourier transform-IR spectra) of prostate tissue taken from younger men (aged 16 to 36 years) and older men (aged 55 to 80 years) as well as prostate tissue spectra from older men with prostate cancer and older men without prostate cancer. They found that there was a highly significant increase in DNA damage (8-hydroxypurine lesions) with advancing age. This damage could be estimated by measuring the concentration of 8-hydroxyguanine in prostate tissue from young and older men. It is known that 8-hydroxyguanine is formed when DNA is attacked by free radicals, specifically hydroxyl radicals.

The researchers also found that they could easily distinguish DNA spectra from older men without prostate cancer from those of older men with prostate cancer. They speculate that the new test may be able to predict the risk of a man developing prostate cancer by determining the extent of free radical damage at any particular point in time. Perhaps the most exciting discovery was the ability of DNA spectra analysis to determine whether the cancer had metastasized well before any damage to other organs actually had occurred.

The researchers conclude that prostate cancer is largely caused by free radical attacks on both the base and backbone structure of DNA. They suggest that an increase in the intake of such dietary antioxidants as vitamin E, lycopene and polyphenols may inhibit the development of prostate cancer.

*Malins, Donald C., et al. Cancer-related changes in prostate DNA as men age and early identification of metastasis in primary prostate tumors*. **Proceedings of the National Academy of Sciences**, *Vol. 100, No. 9, April 29, 2003, pp. 5401-06*

**Editor's comment**: Vitamin C (ascorbic acid) is also an effective scavenger of hydroxyl radicals and helps prevent the formation of 8-hydroxyguanine.

## Exercise and GERD

OKLAHOMA CITY, OKLAHOMA. Many athletes suffer from gastroesophageal reflux disease (GERD) in which stomach contents move into the esophagus causing heartburn (acid reflux). Researchers at the University of Oklahoma now report that weightlifters are considerably more prone to acid reflux than are competitive cyclists and runners. Their experiment involved 10 runners, 10 weightlifters, and 10 cyclists. Each had electrodes placed in their stomach and esophagus enabling continual measurement of acidity (pH) in the two areas. Runners and cyclists exercised for 60 minutes at 65% maximal heart rate and 20 minutes at 85% maximal heart rate. Weightlifters performed a series of weightlifting exercises at 65% of their 1-RM (3 sets) and 85% of their 1-RM (1 set). All exercises were performed in the fasting state as well as 45 minutes after consuming a standard meal.

The severity of acid reflux was measured as the percent of time that the pH at the esophagus electrode was 4.0 or less. Weightlifters experienced the most heartburn, 18.5% of the time in the fasting state and 35.8% after the meal. Cyclists had heartburn 4.0% and 6.5% and runners 4.9% and 17.2% fasting and after the meal respectively. The researchers also measured gastroesophageal reflux, that is, the movement of any stomach content (not just acid) into the esophagus; this was defined as the total time over which the pH in the esophagus was 5.0 or less. For weightlifters the percent of time spent experiencing gastroesophageal reflux was 32.5% (fasting) and 49.3% (after meal). Corresponding figures were 10.4% and 11.5% for cyclists and 8.4% and 26.8% for runners. Surprisingly, reflux was no different in weightlifters whether they were upright or lying down and cyclists, who lean forward on their racing bikes actually had significantly less reflux than did upright runners. This shows that the effect of gravity in helping to keep stomach contents in the stomach is of minor, if any, significance, at least in trained athletes.

*Collings, Kimberly L., et al. Esophageal reflux in conditioned runners, cyclists, and weightlifters*. **Medicine & Science in Sports & Exercise**, *Vol. 35, May 2003, pp. 730-35*

## Serotonin syndrome caused by drug combination

ROCHESTER, NEW YORK. Serotonin syndrome is a serious adverse drug reaction, which most commonly occurs when two or more drugs affecting serotonin synthesis or reuptake are given together or in close succession. It is known that SSRIs (selective serotonin reuptake inhibitors) such as Prozac, Paxil, Effexor, Zoloft, etc. can induce serotonin syndrome. Hospital pharmacists recently reported two cases of serotonin syndrome brought on by a combination of paroxetine (Paxil) and the anti-hallucinatory drug risperidone (Risperdal). The first case involved an 86-year-old man who became increasingly agitated with escalating doses of risperidone (in addition to 10 mg/day of paroxetine). He died 5 days after admission to hospital.

The second case involved a 78-year-old woman who was being treated with paroxetine for depression and risperidone for agitation. Her dose of risperidone was increased to manage agitation following which she developed muscle incoordination, dizziness, and tremor. She was transferred to hospital where the paroxetine and risperidone were withdrawn and she was treated with lorazepam (Ativan). She recovered in two days and was discharged. The pharmacists warn that serotonin syndrome should be considered if a patient shows increased agitation when being treated with SSRIs and increasing doses of risperidone.

*Karki, Shyam D. and Masood, Gule-Rana. Combination risperidone and SSRI-induced serotonin syndrome.* **Annals of Pharmacotherapy**, *Vol. 37, March 2003, pp. 388-91*

# NEWSBRIEFS

**E-nose sniffs out tumours.** Researchers at the University of Rome have developed an electronic device that can predict the presence of lung cancer by analyzing the patient's breath. Several disease conditions result in the production of specific chemical compounds that can be detected in the breath. Lung cancer patients, for example, exhale a mixture of alkanes and benzene derivatives. The e-nose is based on an array of tiny quartz crystals coated with different substances that are capable of absorbing various volatile compounds. The absorption of benzene, for example, by one of the coated crystals will change the vibrational frequency of the crystal thus giving a telltale sign of the presence of benzene. The researchers evaluated 60 people with the new test – 35 lung cancer patients and 25 controls. The test pinpointed every one of the cancer patients. The researchers hope that the test can be refined to the point where it can predict lung cancer even before any tumours are actually formed.

*New Scientist, May 10, 2003, p. 15*

**Serious setback for gene therapy.** Gene therapy has been hailed as the future of medicine and its promise of being able to cure almost any disease provided much of the impetus for the recently completed human genome project. The technique makes use of retroviruses (a class of viruses that can create double-stranded DNA copies of their RNA genomes) to insert normal genes into bone marrow cells to replace the nonfunctional ones. One of the first applications of gene therapy was the attempt to cure a severe, inherited autoimmune disease called X-SCID. Of the 11 boys undergoing gene therapy 2 and perhaps 3 later developed leukemia. Researchers now realize that the retroviruses tend to deliver the new gene to a point near another gene (*Lmo2*), which helps control cell growth and can promote cancer if turned on at the wrong time. The finding has caused the FDA to suspend 27 gene therapy trials and the Great Ormond Street Children's Hospital in London now only treats X-SCID patients with gene therapy if death is otherwise unavoidable.

*New Scientist, March 15, 2003, p. 6*

**Laser-aided drug delivery.** Patients with a chronic illness often need regular medications or drug injections. Researchers at the University of Texas have now developed a new method that allows the delivery of exact doses of drugs as

needed or at specific intervals. The drug is encapsulated in a water-soluble polymer called a hydrogel and then implanted into a convenient spot on the body such as the wrist. Hydrogels have the ability to "leak" the drug into their surroundings when exposed to heat. The researchers developed a wristwatch-like device containing a laser which when activated heats the hydrogel (through the skin) sufficiently to release the drug. Turning off the laser causes the hydrogel to close up again and stop the drug flow. Human trials with the new device will begin in 2005.
*New Scientist, March 22, p. 21*

**Nicotine may promote lung cancer.** Smoking causes lung cancer by triggering pre-cancerous mutations in DNA. Now researchers at the Oregon National Primate Research Center have raised the suspicion that nicotine, a component of cigarette smoke, may make lung cancers more aggressive by stimulating existing tumour cells. The researchers discovered that tumour cells in small cell lung carcinoma posses receptors for the neurotransmitter acetylcholine and also produce large amounts of acetylcholine themselves. When the acetylcholine receptors were blocked with atropine the tumour cells stopped growing. Nicotine is a strong activator of acetylcholine receptors so it is possible that it could help initiate the process whereby the tumours begin producing large amounts of acetylcholine to facilitate their further growth. The researchers now speculate that it may be possible to develop drugs that will stop or at least slow down lung cancer by eliminating acetylcholine production in the cancerous cells.
*New Scientist, March 29, 2003, p. 25*

**Smallpox vaccine lasts a long time**. Researchers at the Oregon Health and Science University report that people vaccinated against smallpox as far back as 1928 still have as many smallpox virus antibodies in their immune system as do those vaccinated recently. They conclude that people vaccinated in childhood are still partly protected as adults.
*New Scientist, May 31, 2003, p. 24*

**MRI scans and pacemakers**. MRI scans use powerful radio waves to generate images of body components and tissue. It is now clear that these radio waves can interfere with implanted pacemakers causing them to heat up (if metals parts are present) or malfunction. Two years ago a patient in a British hospital died after having been given a MRI brain scan when his implanted pacemaker malfunctioned during the procedure. Medical experts point out that the pacemaker leads themselves are also vulnerable as are stents holding open narrowed blood vessels, drug pumps, and nerve stimulators for controlling prostheses. MRI scans should not be given to patients with these kinds of implants.
*New Scientist, May 31, 2003, p. 15*

**Childhood asthma linked to traffic pollution**. A study involving 300,000 Taiwanese school children aged 12 to 15 years concluded that children exposed to heavy traffic pollution have a 16% increased risk of developing allergic rhinitis (hay fever). A smaller study involving 4000 German children concluded that those living within 50 meters of busy roads are twice as likely to show symptoms of asthma as are children living in less polluted areas. Children living in polluted areas are also more likely to suffer from allergies, coughing and sneezing.
*New Scientist, May 31, 2003, p. 7*

# Alzheimer's Disease: What Is Known About Delaying Or Preventing Its Onset Or Progression? – Part I

**by William R. Ware, Emeritus Professor of Chemistry, University of Western Ontario**

## INTRODUCTION

Alzheimer's disease (AD) is one of a number of forms of dementia. According to the commonly used definition, dementia requires an irreversible, global impairment of cognitive skills including memory. The impairment must be great enough to interfere with the activities of daily living (1). Common characteristics of dementia include severe memory loss, inability to formulate abstract thoughts, confusion, problems with

concentrating, difficulty carrying out both routine and complex tasks, personality changes and paranoid or bizarre behavior (2). These characteristics are the result of abnormal brain processes, not age. Up until about 1975 the term Alzheimer's disease or Alzheimer's dementia was reserved for the rare, early onset (40-60 years old) cases of cognitive loss, now known to generally result from a strong genetic predisposition. In fact, the demented patient cared for by Alois Alzheimer in 1901 in Germany was only 51, died in 1905, and the pathology exhibited by her brain was subsequently described and termed "Alzheimer's disease." Beyond the age of 65 loss of cognitive ability was traditionally viewed as a more or less inevitable consequence of aging (1). When it was recognized that presenile and many senile dementias shared a common pathology, dementias in later life finally became a recognized "disease." While conventional wisdom held that problems caused by normal aging were unavoidable, a true disease theoretically should be subject to both treatment and prevention. This had the highly significant consequence of opening the door for research funding (3). Considering AD as a disease had and still has strong political implications, and in the last decade there has been a virtual explosion in both fundamental and clinical research.

Harrison's *Manual of Medicine, 15th Edition,* lists five common causes of dementia and nine additional causes among adults. Thus the physician, when confronted with a patient presenting with signs of dementia, clearly faces a daunting task of differential diagnosis, made especially critical since some causes of dementia are treatable and even curable. It is in fact easy to argue that sooner rather than later specialized assessment from a neurologist or a specialist in neuropsychiatry, or both, is highly desirable, not only to avoid the calamity of leaving untreated a curable mental disease but also to identify as early as possible the cause of the dementia in order that therapeutic and delaying tactics can be initiated, even if the underlying disease is in fact judged incurable. A complete medical work-up is also needed to rule out potentially treatable causes of dementia such as encephalopathy, intracranial mass (e.g. tumor), infections that cause dementia, endocrine problems such as an under active thyroid, over-medication, metabolic problems, etc. Depression and delirium can mimic dementia, and are also treatable (2).

AD and vascular dementia (VaD) and a mixture of the two (mixed dementia) appear to be the most common forms, and this review will be restricted to these. The prevalence of dementia in community dwelling individuals over the age of 65 is estimated to be from 6-8%, whereas for those in nursing homes and chronic care facilities, the number can be as high as 75%. Prevalence of AD doubles approximately every 5 years after age 60. It is estimated that at least 30% of the US population over 85 has AD. While disease progression can be delayed, and in a few cases to be discussed below, dramatic reversals have been achieved, the normal course is a steady decline in almost all aspects associated with the "quality of life." For example, the inability to find the way home may be followed by the inability to fine some room in a home occupied for, perhaps, decades. At this stage there are frequently serious disruptive psychological problems as the individual understandably fails to cope with the disability. Resultant behavioral problems may require aggressive intervention with behavior modifying drugs in order for the individual to continue to live at home. Profound depression is also very common. Eventually there is the loss of control of bodily functions, especially urinary control, the loss of the ability to recognize family members, and finally total incapacitation. The average time from diagnosis of AD to death depends on age. Researchers from Johns Hopkins University found that patients diagnosed with AD in their 60s or 70s have a median remaining lifespan of 7-10 years, whereas those diagnosed in their 90s have a median remaining lifespan of only approximately 3 years (4). Studies suggest that dementia is an underlying but not necessarily primary cause of death. In fact, some studies find that the immediate causes of death are similar in demented and non-demented hospitalized elderly (5). However, individuals with VaD have an increased risk of death due to cardiovascular disease and in particular heart failure when compared to patients with AD (5).

It is common for individuals to seek out professional advice before the symptoms of AD or dementia are present. Generally the complaint relates to memory problems that have become bothersome or have caused as spouse or family member to suggest evaluation. This is covered below under the heading "Mild Cognitive Impairment."

The term *Alzheimer's disease*, while widely used, has a number of different connotations and modern usage has attempted to clarify the exact meaning. Thus today it is common to see the following definitions (6):

- **Definite AD**. Presence of clinical characteristics of AD confirmed by histopathological evidence, generally from postmortem study of brain tissue. In the simplest terms, a diagnosis of definite AD requires the patient to already be dead! This state of affairs underlines the difficulty of a definite diagnosis based only on clinical observations (when one is alive). The pathological features that constitute the so-called hall-marks of AD are senile plaques and neurofibrillary tangles, two distinctive formations in brain tissue. Finding them in large numbers at postmortem is taken by most pathologists as proof of AD. Finding them in profusion in the brains of totally non-demented individuals is another matter, and one which illustrates the complexity of this disease.
- **Probable AD**. Diagnosis is established by clinical examination and an evaluation of mental status via a history and tests. Probable AD is generally defined as requiring deficits in two or more areas of cognition. Dementia must be present. There should be progressive worsening of memory and other cognitive functions. Systemic or other brain diseases that also produce dementia should be ruled out. Normally, the age of onset is between 40 and 90. AD at a young age usually implies a strong genetic or family connection, since in the general population AD is rare prior to about age 60.

Because the neuropathological or histopathological manifestations of AD can occur without producing dementia, it has been suggested (1) that the terms “Alzheimer’s disease” and “Alzheimer’s dementia” should be used, the former referring to the presence of the neuropathologic characteristics and the latter requiring both the neuropathology and dementia. Both terms obviously require post mortem evidence.

Criteria for vascular dementia are also categorized by “definite” and “probable” as follows (6):

- **Definite VaD**. Clinical criteria for probable VaD. Autopsy demonstration of appropriate ischemic or hemorrhagic (bleeding) brain injury. No other causes of dementia.
- **Probable VaD.** Based on clinical evaluation. Decline in cognitive functioning. Deficits severe enough to interfere with the activities of daily living. Absence of any other disorder capable of producing dementia is required. VaD can be related to the effects of a stroke, and a diagnostic factor is neuroimaging evidence of extensive vascular lesions.

It should be noted that neuroimaging (MRI, PET, or single photon emission CT) is becoming a particular valuable tool for the differential diagnosis of dementia (7, 8). Clinical features also allow to some extent the differentiation of VaD and AD (6). VaD can evolve in a stepwise fashion following transient ischemic attacks that are really mini-strokes. They may be accompanied by various frequently vague and transitory symptoms such as light-headedness, dizziness, visual disturbance, headache, or mild tingling of the extremities (9). Also, the development of atherosclerosis over many years can slowly decrease the blood supply to the brain with associated cell damage and cell death due to oxygen and glucose deprivation, resulting eventually in VaD. The dementia can also occur after a sudden, paralyzing stroke. In some cases, post-stroke dementia can be prevented by appropriate treatment (9)

As the population age distribution shifts to older individuals, it is clear that a huge personal and financial burden is looming. While there is a high level of interest among the general public regarding the results and promise of anti-aging research, life extension will be a mixed blessing unless the problem of dementia is solved. It has been estimated that AD afflicts about 15 million people worldwide with about 4 million in the US alone (10). In the absence of a cure or a successful preventative protocol, it is estimated that 14 million Americans will develop AD by 2050 (11). It thus comes as no surprise that one of the most active areas of medical research today, both from the clinical and basic science perspective, involves finding the causes and devising treatments for AD. A literature search using the key word “Alzheimer” brings up about 3000 medical journal references just for the year 2002!

## WHAT IS THE CAUSE OF ALZHEIMER’S DISEASE?

The short answer is that nobody really knows for sure. A more detailed answer depends on not only what is meant by the word *cause* but also how one separates suspected primary causes from effects that by default tend to be viewed as causes. For example, epidemiologic studies (12, 13) suggest that long-term use of

non-steroidal anti-inflammatory drugs (NSAIDs) reduces the incidence of AD in some populations. Can one conclude from this that inflammation actually causes AD? Perhaps inflammation simply contributes to or aggravates some more fundamental causative process. So-called plaques and tangles, the pathological hallmarks of AD, are frequently referred to as the "causes" of AD, but what causes the plaques and tangles? And how does one explain patients totally free of dementia whose brains exhibit large numbers of plaques and tangles? These problems are swept under the rug in some discussions of AD and its etiology, but careful reading of the literature will reveal a number of scientists and clinicians who raise serious questions regarding the conventional wisdom and endeavor to encourage a view which recognizes the multi-factorial nature of the disease.

The conventional wisdom regarding the cause of AD focuses on what is termed the Amyloid Cascade Hypothesis (ACH). In this model, something goes wrong with the metabolism associated with so-called amyloid precursor protein (APP), and the fragments derived from it. These fragments, called amyloid beta or Aβ for short, then exhibit an abnormal tendency to aggregate yielding the so-called senile plaques that are seen in AD brains at autopsy. At the same time, something goes wrong with another protein called tau, which leads to the neurofibrillary tangles also seen in the AD brain.

The neuron looks something like an octopus with branches (dendrites) protruding from the central body, one of which, called the axon, is much longer than the others. The axon makes contact and communicates with other neurons through contact (synapses) to the dendrite of another neuron. The AD tangles form in the axon, blocking the flow of nutrients to the nerve endings and interrupting communications inside the cell and eventually killing it. The amyloid plaque that forms at the axon-dendrite contact points inhibits communication and induces an inflammatory reaction, and eventually killing healthy synapses and cells around the plaque. Thus the ACH regards Aβ and the plaques as neurotoxic and responsible in part for the death of neurons and the loss of cognitive ability. In the earliest clinical phase, AD is characterized by an almost pure memory impairment, which is thought to be due to synaptic dysfunction caused by Aβ (14). What actually triggers these problems with APP, Aβ and tau does not seem very clear, nor is there proof that these plaques and tangles directly cause the clinical symptoms of the disease. There appears to be general agreement however, that the dementia is due to the cumulative effect of the death of neurons and the failure of signaling pathways. Some believe that oxidative stress produced by an excess of highly reactive free radicals may play a role in the initiation process. Other theories view inflammation as a trigger or factor, and as well, restricted cerebral blood flow is a frequently cited causative factor. Toxins are also implicated. There are those who believe that both neurotoxicity and neuroprotective process are at work with tau and Aβ, and that Aβ may actually be neuroprotective in some of its forms and at some stage in it production (15).

The ACH has led to potential therapies. A vaccine for Aβ which causes the break-up of senile plaques and the clearance of Aβ in mice has been developed by a pharmaceutical company. Human trials were recently halted due to the incidence of a serious inflammatory disorder of the central nervous system observed in a few participants in the trial, a halt that came before any changes in clinical symptoms could be evaluated with statistical significance. If the vaccine had reduced the plaque burden and resulted in clinical improvement, this would have gone a long way toward establishing the merits of the ACH. But this is not to be, at least in the foreseeable future. Pharmaceutical companies are also working on inhibitors for the enzymes that chop off the Aβ fragments from the APP, but nobody knows what the overall effects of this type of inhibition might be, since these enzymes have other actions in human biochemistry. The Amyloid Cascade Hypothesis has had a big impact on the direction of therapeutic research, in fact it has dominated it. If the hypothesis is flawed or seriously incomplete, as some think, then considerable time and vast sums of money have been spent, both in academic and pharmaceutical settings, going down only one road, so to speak, at the expense of considering and developing therapeutic alternatives not based on the ACH.

In the view of some neuroscientists the causes and the mechanism of progression of AD are much more complex than is implied by the Amyloid Cascade Hypothesis. Considerable attention is now focused on the significance of the large variety of vascular abnormalities that are also frequently present in the AD brain. In addition, there is the fundamental question of the relationship between the ultimate causes of AD and the many types of cerebral vascular disease. In fact, it has been recognized for some time that AD and vascular disease share many epidemiologic risk factors (16, 17). In a paper recently published in the journal *Stroke*, de la Torre (18) provides an interesting list of reported risk factors for AD from epidemiologic studies on

elderly subjects. Included are atherosclerosis, stroke, diabetes, smoking, high cholesterol, cardiac disease, high serum viscosity, thrombogenic factors, high serum homocysteine, hypertension and hypotension, high fibrinogen levels, and transient ischemic attacks, all of which point to the involvement of vascular disorders. His thesis is that AD, when not caused by a strong genetic predisposition (the early onset type of AD), is initiated by vascular factors that precede the neurodegenerative process. This conclusion he claims is consistent with most of the basic and clinicopathologic data reported for AD, and is not inconsistent with other findings which indicate neurodegenerative processes as the cause of this disorder (18, 19). It has in fact been proposed recently that VaD is the most common form of dementia in the elderly (20), but some studies do not find this to be the case. A detailed discussion of vascular risk factors for AD from an epidemiologic perspective can also be found in a recent review by Breteler (21).

While clinical diagnostic protocols attempt to differentiate AD and VaD (6), and pure AD requires by definition the absence of vascular disease deemed serious enough to cause dementia, it seems clear (17) that in fact not only do AD and VaD share many of the same clinical signs and symptoms, but that the pure forms may represent two extremes of a continuum of pathology. If one looks at the prevalence of common pathological lesions in AD and VaD, many are frequently seen together at significant levels of incidence. Studies suggesting that the biochemistry that leads to plaque formation can be induced in part by vascular disease further justifies the continuum notion by extending it to factors that may be closely related to the ultimate causes (18, 19). de La Torre (22) actually would like to see AD classified as a vascular disorder. He considers that this would likely improve the chances of finding useful treatments because clinical studies could focus on more realistic and relevant pathologic targets than at present.

A recent article in *The New England Journal of Medicine* (23) underscores the connection between vascular disease and dementia. The study deals with the risk of dementia and cognitive decline associated with so-called silent brain infarcts, which in this context were mini-strokes that went unnoticed by the individual. The effects were seen with MRI imaging, identified if present at baseline, and followed for a number of years with repeated imaging. Neuropsychological assessment was used to establish the presence of dementia and cognitive decline. A significant finding was that silent brain infarcts increased not only the risk of dementia, but also that in this study the majority of cases that occurred were of the Alzheimer subtype. In an accompanying editorial in the same issue, Blass and Ratan point out that such studies provide guidance in intervention because recommendations can be based on the large body of well documented evidence concerning the prevention of vascular disease (24).

Further evidence for the view that the pathological basis for AD has many unresolved issues was recently presented by Vagnucci and Li in the journal *Lancet* (13). They present a fascinating table that summarizes the relative risk reduction of AD found in high-risk populations resulting from the use of a number of different drugs, including NSAIDs, steroids, histamine H2 blockers (such as Pepcid AC, or Zantac), calcium channel blockers, and lipid lowering agents (statins). Relative risk reductions as low as 0.14 were found for H2 blockers, with most relative risk numbers well below 0.5. These are impressive risk reductions by any standard, and yet the drugs obviously had quite different primary actions, as defined by the indications normally calling for their use (abnormal blood lipid profile, hypertension, heart burn, inflammation from arthritis, etc.). Vagnucci and Li suggest that the connecting factor for the action of this set of drugs, while not excluding other actions, is antiangiogenic activity (inhibition of neovascularization). In their view, AD in part involves the activation of large populations of endothelial cells by angiogenesis due to inflammation and oxygen deprivation. These cells are thought to be involved in the secretion of precursor substrate for Aβ and a neurotoxic peptide that selectively kills neurons. They advance the hypothesis that the drugs listed above have antiangiogenesis actions which inhibit this mechanism of neurotoxicity. Considerable evidence is presented for this hypothesis, which may eventually stimulate drug design and clinical trials. The point, however, is how little is really know about the details of what appear to be the highly complex pathological phenomena that ultimately cause AD.

## MILD COGNITIVE IMPAIRMENT—AN EARLY WARNING SIGNAL?

Historically, forgetfulness among the elderly was simply considered a normal consequence of aging. Various descriptive, pseudo-medical terms were used (25), including *benign senescent forgetfulness*, *age-*

*associated memory impairment, late-life forgetfulness*, etc. However, it has always been possible to find examples of individuals in their 90s or even over a hundred who were most certainly not demented, had little if any cognitive or memory decline, and who were capable of independent living, balancing their checkbook, playing cards, etc. It is interesting that these fortunate individuals were frequently devoid of coexisting disorders, such as diabetes, hypertension, coronary artery disease and sensory abnormalities, any or all of which might accompany "typical" aging (26). Today the term *Mild Cognitive Impairment* (MCI) is frequently used to describe serious memory problems.

There are a number of causes of (MCI) other than a pre-Alzheimer disorder. These include depression, mini-strokes, alcoholism, vitamin deficiency, low thyroid levels, overmedication, and sleep problems (27). According to Dr. Majid Fotuhi of Harvard Medical School, the majority of people who have memory problems and fear that they have AD may be experiencing the symptoms of depression and are in fact surprised to learn that depression can be viewed as a brain disease (27). Depression is treatable and patients can regain both their memory and a good outlook on life. Just as in the case of AD, it is critical to exclude these other causes of MCI when evaluating a patient with a memory complaint.

In recent years growing attention has been given to the possibility that memory problems of the elderly, both self-reported and observed by spouses or relatives, may be a useful and reliable predictor of the future risk of developing dementia, including AD. The central problem with studies directed at this important question has to do with the definition and diagnosis of MCI. The perception of memory problems differs considerably from individual to individual, and may not always be consistent with that noticed by an observer. In addition, some studies include in the definition of MCI one other aspect of cognitive impairment, so on the one hand there is the so called *amnesic* MCI, which is just a memory abnormality, and on the other a combination of amnesic MCI and an additional cognitive deficit. An important aspect of all definitions of MCI is the absence of dementia. Sometimes, the assessment is made with a battery of tests, sometimes just with a history and questions. A distinguishing feature of MCI as compared to age-associated memory impairment (normal) is that individuals with the latter do not get worse rapidly—they frequently complain of the same degree of memory problems for a number of years. However, this is not clear cut, and some individuals thought to have MCI actually get better or do not progress to AD.

Evidence from a number of studies does indeed suggest that the presence of MCI significantly increases the probability of developing AD. The increased risk depends on just how MCI is defined, and how accurate the definition matches the patient. It is unclear whether amnesic MCI or MCI with an added cognitive impairment has a greater risk of progressing to AD, although the evidence is in favor of a greater risk for the latter. Recent studies indicate that persons with MCI have as high as a 50% probability of developing AD sometime in the 4 years following the initial diagnosis (26). One study found an annual conversion rate of 8.3%, which is about 38% over four years (28). A study organized by the Mayo Clinic found an annual rate of conversion of 10-12% per year for amnesic MCI patients characterized by a memory complaint abnormal for their age, but with normal activities of daily living, normal general cognitive function, and the absence of dementia (29). In normal subjects one expects less that 2% conversion per year for the group in question. While studies yielding smaller conversion rates than 8-12% per year can be found, it is nevertheless clear that MCI, even when defined to involve just a memory problem, indicates a potential risk that is significant.

Studies have been reported where individuals classified as having MCI but no dementia have for some reason died and their brains have been examined. There are also cases where the brains of individuals free of any signs of MCI have been examined for evidence of AD pathology. What is perhaps surprising is that there were a number of individuals in these two groups where the pathology of AD was clearly and abundantly evident, and yet they showed no signs of dementia (30, 31). In other words, the pathology of AD can presumably develop, in some cases extensively, while the individual remains asymptomatic or develops only MCI. This may be related to the rather short interval between patients presenting with MCI and the development of clear clinical evidence for probable AD, at least for those in which this is indeed the sequence of events (32). In other words, the AD pathology appears to develop over an extended period prior to the MCI diagnosis. Also, in other studies of groups classified as having MCI, a significant percentage have, after several years, reverted to normal, for no apparent reason, even though progression to AD was seen in other members of the cohort (28, 33). Some researchers (32) like to view these early stages as a continuum, where at the beginning there can be AD pathology, or perhaps vascular pathology, or both, and

later on MCI can develop, followed by the development of the clinical symptoms of AD. But up to some point the process or processes may either slow, halt, or even reverse without intervention. This broad view is very important because symptoms of MCI, especially amnesic MCI, need not necessarily mean that AD is inevitable.

**References**


1. Blass, J. P., "Alzheimer's disease and Alzheimer's dementia: distinct but overlapping entities," *Neurobiol.Aging*, Vol. 23, No. 6, 2002, pp. 1077-1084.
2. Mayo Clinic on Alzheimer's Disease. Petersen, R. 2002. New York, Mayo Clinic Health Information.
3. Morgan, D., "The intersection of Alzheimer's disease and typical aging," *Neurobiol.Aging*, Vol. 22, No. 1, 2001, pp. 159-160.
4. Brookmeyer, R., Corrada, M. M., Curriero, F. C., and Kawas, C., "Survival following a diagnosis of Alzheimer disease," *Arch.Neurol.*, Vol. 59, No. 11, 2002, pp. 1764-1767.
5. Kammoun, S., Gold, G., Bouras, C., Giannakopoulos, P., McGee, W., Herrmann, F., and Michel, J. P., "Immediate causes of death of demented and non-demented elderly," *Acta Neurol.Scand.Suppl*, Vol. 176, 2000, pp. 96-99.
6. Cummings, J. L.. Neuropsychiatry of Alzheimer's Disease and Related Dementia. 2003. London, Martin Dunlitz.
7. Petrella, J. R., Coleman, R. E., and Doraiswamy, P. M., "Neuroimaging and early diagnosis of Alzheimer disease: a look to the future," *Radiology*, Vol. 226, No. 2, 2003, pp. 315-336.
8. Felber, S. R., "Magnetic resonance in the differential diagnosis of dementia," *J Neural Transm.*, Vol. 109, No. 7-8, 2002, pp. 1045-1051.
9. Cohen, E.. Alzheimer's Disease. 1999. Los Angeles, Keats Publishing.
10. Mayeux, R. and Sano, M., "Treatment of Alzheimer's disease," *The New England Journal of Medicine*, Vol. 341, No. 22, 1999, pp. 1670-1679.
11. Brookmeyer, R., Gray, S., and Kawas, C., "Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset," *Am J Public Health*, Vol. 88, No. 9, 1998, pp. 1337-1342.
12. in, t., V, Ruitenberg, A., Hofman, A., Launer, L. J., van Duijn, C. M., Stijnen, T., Breteler, M. M., and Stricker, B. H., "Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease," *The New England Journal of Medicine*, Vol. 345, No. 21, 2001, pp. 1515-1521.
13. Vagnucci, A. H., Jr. and Li, W. W., "Alzheimer's disease and angiogenesis," *Lancet*, Vol. 361, No. 9357, 2003, pp. 605-608.
14. Selkoe, D. J., "Alzheimer's disease is a synaptic failure," *Science*, Vol. 298, No. 5594, 2002, pp. 789-791.
15. Robinson, S. R. and Bishop, G. M., "Abeta as a bioflocculant: implications for the amyloid hypothesis of Alzheimer's disease," *Neurobiol.Aging*, Vol. 23, No. 6, 2002, pp. 1051-1072.
16. Royall, D. R., "Alzheimer disease as a vascular disorder: nosological evidence," *Stroke*, Vol. 33, No. 9, 2002, pp. 2147-2148.
17. Kalaria, R., "Similarities between Alzheimer's disease and vascular dementia," *J Neurol.Sci*, Vol. 203-204, 2002, pp. 29-34.
18. de la Torre, J. C., "Alzheimer disease as a vascular disorder: nosological evidence," *Stroke*, Vol. 33, No. 4, 2002, pp. 1152-1162.
19. de la Torre, J. C., "Impaired cerebromicrovascular perfusion. Summary of evidence in support of its causality in Alzheimer's disease," *Ann N Y.Acad Sci*, Vol. 924, 2000, pp. 136-152.
20. Roman, G. C., "Vascular dementia may be the most common form of dementia in the elderly," *J Neurol.Sci*, Vol. 203-204, 2002, pp. 7-10.
21. Breteler, M. M., "Vascular risk factors for Alzheimer's disease: an epidemiologic perspective," *Neurobiol.Aging*, Vol. 21, No. 2, 2000, pp. 153-160.
22. de la Torre, J. C., "Alzheimer's disease: How does it start?," *J Alzheimers.Dis.*, Vol. 4, No. 6, 2002, pp. 497-512.
23. Vermeer, S. E., Prins, N. D., den Heijer, T., Hofman, A., Koudstaal, P. J., and Breteler, M. M., "Silent brain infarcts and the risk of dementia and cognitive decline," *The New England Journal of Medicine*, Vol. 348, No. 13, 2003, pp. 1215-1222.
24. Blass, J. P. and Ratan, R. R., ""Silent" strokes and dementia," *The New England Journal of Medicine*, Vol. 348, No. 13, 2003, pp. 1277-1278.
25. Ritchie, K. and Touchon, J., "Mild cognitive impairment: conceptual basis and current nosological status," *Lancet*, Vol. 355, No. 9199, 2000, pp. 225-228.
26. Shah, Y., Tangalos, E. G., and Petersen, R. C., "Mild cognitive impairment. When is it a precursor to Alzheimer's disease?," *Geriatrics*, Vol. 55, No. 9, 2000, pp. 62, 65-62, 68.
27. Fotuhi, M.. The Memory Cure. 2003. New York, McGraw Hill.

28. Larrieu, S., Letenneur, L., Orgogozo, J. M., Fabrigoule, C., Amieva, H., Le Carret, N., Barberger-Gateau, P., and Dartigues, J. F., "Incidence and outcome of mild cognitive impairment in a population-based prospective cohort," *Neurology*, Vol. 59, No. 10, 2002, pp. 1594-1599.
29. Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E., "Mild cognitive impairment: clinical characterization and outcome," *Arch.Neurol.*, Vol. 56, No. 3, 1999, pp. 303-308.
30. Price, J. L., Ko, A. I., Wade, M. J., Tsou, S. K., McKeel, D. W., and Morris, J. C., "Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease," *Arch.Neurol.*, Vol. 58, No. 9, 2001, pp. 1395-1402.
31. Snowdon, D. A., "Aging and Alzheimer's disease: lessons from the Nun Study," *Gerontologist*, Vol. 37, No. 2, 1997, pp. 150-156.
32. Burns, A. and Zaudig, M., "Mild cognitive impairment in older people," *Lancet*, Vol. 360, No. 9349, 2002, pp. 1963-1965.
33. Palmer, K., Wang, H. X., Backman, L., Winblad, B., and Fratiglioni, L., "Differential Evolution of Cognitive Impairment in Nondemented Older Persons: Results From the Kungsholmen Project," *American Journal of Psychiatry*, Vol. 159, No. 3, 2002, pp. 436-442.
34. O'Meara, E. S., Kukull, W. A., Sheppard, L., Bowen, J. D., McCormick, W. C., Teri, L., Pfanschmidt, M., Thompson, J. D., Schellenberg, G. D., and Larson, E. B., "Head injury and risk of Alzheimer's disease by apolipoprotein E genotype," *Am J Epidemiol.*, Vol. 146, No. 5, 1997, pp. 373-384.
35. Guo, Z., Cupples, L. A., Kurz, A., Auerbach, S. H., Volicer, L., Chui, H., Green, R. C., Sadovnick, A. D., Duara, R., DeCarli, C., Johnson, K., Go, R. C., Growdon, J. H., Haines, J. L., Kukull, W. A., and Farrer, L. A., "Head injury and the risk of AD in the MIRAGE study," *Neurology*, Vol. 54, No. 6, 2000, pp. 1316-1323.
36. Esposito, E., Rotilio, D., Di, M., V, Di Giulio, C., Cacchio, M., and Algeri, S., "A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes," *Neurobiol.Aging*, Vol. 23, No. 5, 2002, pp. 719-735.
37. Engelhart, M. J., Geerlings, M. I., Ruitenberg, A., van Swieten, J. C., Hofman, A., Witteman, J. C., and Breteler, M. M., "Dietary intake of antioxidants and risk of Alzheimer disease," *JAMA*, Vol. 287, No. 24, 2002, pp. 3223-3229.
38. Grundman, M., Grundman, M., and Delaney, P., "Antioxidant strategies for Alzheimer's disease," *Proc.Nutr Soc.*, Vol. 61, No. 2, 2002, pp. 191-202.
39. Martin, A., "Antioxidant vitamins E and C and risk of Alzheimer's disease," *Nutr Rev.*, Vol. 61, No. 2, 2003, pp. 69-73.
40. Seshadri, S., Beiser, A., Selhub, J., Jacques, P. F., Rosenberg, I. H., D'Agostino, R. B., Wilson, P. W., and Wolf, P. A., "Plasma homocysteine as a risk factor for dementia and Alzheimer's disease," *The New England Journal of Medicine*, Vol. 346, No. 7, 2002, pp. 476-483.
41. Payette, H., Boutier, V., Coulombe, C., and Gray-Donald, K., "Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial," *J Am Diet.Assoc.*, Vol. 102, No. 8, 2002, pp. 1088-1095.
42. Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Aggarwal, N., Wilson, R. S., and Scherr, P. A., "Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study," *JAMA*, Vol. 287, No. 24, 2002, pp. 3230-3237.
43. Hofman, A., Ott, A., Breteler, M. M., Bots, M. L., Slooter, A. J., van Harskamp, F., van Duijn, C. N., Van Broeckhoven, C., and Grobbee, D. E., "Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study," *Lancet*, Vol. 349, No. 9046, 1997, pp. 151-154.
44. Korol, D. L., "Enhancing cognitive function across the life span," *Ann N Y.Acad Sci*, Vol. 959, 2002, pp. 167-179.
45. Small, G. W., "Brain-imaging surrogate markers for detection and prevention of age-related memory loss," *J Mol.Neurosci.*, Vol. 19, No. 1-2, 2002, pp. 17-21.
46. Peila, R., Rodriguez, B. L., and Launer, L. J., "Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study," *Diabetes*, Vol. 51, No. 4, 2002, pp. 1256-1262.
47. Stewart, R. and Liolitsa, D., "Type 2 diabetes mellitus, cognitive impairment and dementia," *Diabet.Med*, Vol. 16, No. 2, 1999, pp. 93-112.
48. Convit, A., Wolf, O. T., Tarshish, C., and de Leon, M. J., "Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly," *Proc.Natl.Acad Sci U.S.A*, Vol. 100, No. 4, 2003, pp. 2019-2022.
49. Strachan, M. W., Frier, B. M., and Deary, I. J., "Type 2 diabetes and cognitive impairment," *Diabet.Med*, Vol. 20, No. 1, 2003, pp. 1-2.
50. Yanagisawa, K., "Cholesterol and pathological processes in Alzheimer's disease," *J Neurosci.Res.*, Vol. 70, No. 3, 2002, pp. 361-366.
51. Jick, H., Zornberg, G. L., Jick, S. S., Seshadri, S., and Drachman, D. A., "Statins and the risk of dementia," *Lancet*, Vol. 356, No. 9242, 2000, pp. 1627-1631.

52. Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. G., and Siegel, G., "Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors," *Arch.Neurol.*, Vol. 57, No. 10, 2000, pp. 1439-1443.
53. Kivipelto, M., Helkala, E. L., Hanninen, T., Laakso, M. P., Hallikainen, M., Alhainen, K., Soininen, H., Tuomilehto, J., and Nissinen, A., "Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study," *Neurology*, Vol. 56, No. 12, 2001, pp. 1683-1689.
54. Notkola, I. L., Sulkava, R., Pekkanen, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P., Tuomilehto, J., and Nissinen, A., "Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease," *Neuroepidemiology*, Vol. 17, No. 1, 1998, pp. 14-20.
55. Wolozin, B., "Cholesterol and Alzheimer's disease," *Biochem.Soc.Trans.*, Vol. 30, No. 4, 2002, pp. 525-529.
56. Whyte, E. M., Mulsant, B. H., Butters, M. A., Qayyum, M., Towers, A., Sweet, R. A., Klunk, W., Wisniewski, S., and DeKosky, S. T., "Cognitive and behavioral correlates of low vitamin B12 levels in elderly patients with progressive dementia," *Am J Geriatr.Psychiatry*, Vol. 10, No. 3, 2002, pp. 321-327.
57. Mattson, M. P., Kruman, I. I., and Duan, W., "Folic acid and homocysteine in age-related disease," *Ageing Res.Rev.*, Vol. 1, No. 1, 2002, pp. 95-111.
58. Selhub, J., Bagley, L. C., Miller, J., and Rosenberg, I. H., "B vitamins, homocysteine, and neurocognitive function in the elderly," *American Journal of Clinical Nutrition*, Vol. 71, No. 2, 2000, pp. 614S-620S.
59. Johnson, M. A., Hawthorne, N. A., Brackett, W. R., Fischer, J. G., Gunter, E. W., Allen, R. H., and Stabler, S. P., "Hyperhomocysteinemia and vitamin B-12 deficiency in elderly using Title IIIc nutrition services," *American Journal of Clinical Nutrition*, Vol. 77, No. 1, 2003, pp. 211-220.
60. Wang, H. X., Wahlin, A., Basun, H., Fastbom, J., Winblad, B., and Fratiglioni, L., "Vitamin B(12) and folate in relation to the development of Alzheimer's disease," *Neurology*, Vol. 56, No. 9, 2001, pp. 1188-1194.
61. Clarke, R., Smith, A. D., Jobst, K. A., Refsum, H., Sutton, L., and Ueland, P. M., "Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease," *Arch.Neurol.*, Vol. 55, No. 11, 1998, pp. 1449-1455.
62. Snowdon, D. A., Tully, C. L., Smith, C. D., Riley, K. P., and Markesbery, W. R., "Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the Nun study," *American Journal of Clinical Nutrition*, Vol. 71, No. 4, 2000, pp. 993-998.
63. Miller, J. W., "Vitamin B12 deficiency, tumor necrosis factor-alpha, and epidermal growth factor: a novel function for vitamin B12?," *Nutr Rev.*, Vol. 60, No. 5 Pt 1, 2002, pp. 142-144.
64. Weir, D. G. and Molloy, A. M., "Microvascular disease and dementia in the elderly: are they related to hyperhomocysteinemia?," *American Journal of Clinical Nutrition*, Vol. 71, No. 4, 2000, pp. 859-860.
65. Conquer, J. A., Tierney, M. C., Zecevic, J., Bettger, W. J., and Fisher, R. H., "Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment," *Lipids*, Vol. 35, No. 12, 2000, pp. 1305-1312.
66. Kyle, D. J., Schaefer, E., Patton, G., and Beiser, A., "Low serum docosahexaenoic acid is a significant risk factor for Alzheimer's dementia," *Lipids*, Vol. 34 Suppl, 1999, pp. S245.
67. Tully, A. M., Roche, H. M., Doyle, R., Fallon, C., Bruce, I., Lawlor, B., Coakley, D., and Gibney, M. J., "Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study," *Br.J Nutr*, Vol. 89, No. 4, 2003, pp. 483-489.
68. Kalmijn, S., Launer, L. J., Ott, A., Witteman, J. C., Hofman, A., and Breteler, M. M., "Dietary fat intake and the risk of incident dementia in the Rotterdam Study," *Ann Neurol.*, Vol. 42, No. 5, 1997, pp. 776-782.
69. Yehuda, S., Rabinovitz, S., Carasso, R. L., and Mostofsky, D. I., "The role of polyunsaturated fatty acids in restoring the aging neuronal membrane," *Neurobiol.Aging*, Vol. 23, No. 5, 2002, pp. 843-853.
70. Suter, O. C., Sunthorn, T., Kraftsik, R., Straubel, J., Darekar, P., Khalili, K., and Miklossy, J., "Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease," *Stroke*, Vol. 33, No. 8, 2002, pp. 1986-1992.
71. Zuccala, G., Onder, G., Pedone, C., Carosella, L., Pahor, M., Bernabei, R., and Cocchi, A., "Hypotension and cognitive impairment: Selective association in patients with heart failure," *Neurology*, Vol. 57, No. 11, 2001, pp. 1986-1992.
72. Harrington, F., Saxby, B. K., McKeith, I. G., Wesnes, K., and Ford, G. A., "Cognitive performance in hypertensive and normotensive older subjects," *Hypertension*, Vol. 36, No. 6, 2000, pp. 1079-1082.
73. Morris, M. C., Scherr, P. A., Hebert, L. E., Glynn, R. J., Bennett, D. A., and Evans, D. A., "Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study," *Arch.Neurol.*, Vol. 58, No. 10, 2001, pp. 1640-1646.
74. Posner, H. B., Tang, M. X., Luchsinger, J., Lantigua, R., Stern, Y., and Mayeux, R., "The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function," *Neurology*, Vol. 58, No. 8, 2002, pp. 1175-1181.
75. Peters, R., "The prevention of dementia," *J Cardiovasc.Risk*, Vol. 8, No. 5, 2001, pp. 253-256.
76. Kilander, L., Nyman, H., Boberg, M., Hansson, L., and Lithell, H., "Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men," *Hypertension*, Vol. 31, No. 3, 1998, pp. 780-786.

77. Forette, F., Seux, M. L., Staessen, J. A., Thijs, L., Babarskiene, M. R., Babeanu, S., Bossini, A., Fagard, R., Gil-Extremera, B., Laks, T., Kobalava, Z., Sarti, C., Tuomilehto, J., Vanhanen, H., Webster, J., Yodfat, Y., and Birkenhager, W. H., "The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study," *Arch.Intern.Med*, Vol. 162, No. 18, 2002, pp. 2046-2052.
78. Amenta, F., Mignini, F., Rabbia, F., Tomassoni, D., and Veglio, F., "Protective effect of anti-hypertensive treatment on cognitive function in essential hypertension: analysis of published clinical data," *J Neurol.Sci*, Vol. 203-204, 2002, pp. 147-151.
79. Mukamal, K. J., Kuller, L. H., Fitzpatrick, A. L., Longstreth, W. T., Jr., Mittleman, M. A., and Siscovick, D. S., "Prospective study of alcohol consumption and risk of dementia in older adults," *JAMA*, Vol. 289, No. 11, 2003, pp. 1405-1413.
80. Russo, A., Palumbo, M., Aliano, C., Lempereur, L., Scoto, G., and Renis, M., "Red wine micronutrients as protective agents in Alzheimer-like induced insult," *Life Sci*, Vol. 72, No. 21, 2003, pp. 2369-2379.
81. Ruitenberg, A., van Swieten, J. C., Witteman, J. C., Mehta, K. M., van Duijn, C. M., Hofman, A., and Breteler, M. M., "Alcohol consumption and risk of dementia: the Rotterdam Study," *Lancet*, Vol. 359, No. 9303, 2002, pp. 281-286.
82. Truelsen, T., Thudium, D., and Gronbaek, M., "Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study," *Neurology*, Vol. 59, No. 9, 2002, pp. 1313-1319.
83. Willett, W. C.. Eat, Drink and Be Healthy. The Harvard Medical School Guide to Healthy Eating. 2001. Fireside, New York.
84. Schmidt, R., Schmidt, H., and Fazekas, F., "Vascular risk factors in dementia," *J Neurol.*, Vol. 247, No. 2, 2000, pp. 81-87.
85. Ott, A., Breteler, M. M., de Bruyne, M. C., van Harskamp, F., Grobbee, D. E., and Hofman, A., "Atrial fibrillation and dementia in a population-based study. The Rotterdam Study," *Stroke*, Vol. 28, No. 2, 1997, pp. 316-321.
86. Sabatini, T., Barbisoni, P., Rozzini, R., and Trabucchi, M., "Hypotension and cognitive impairment: selective association in patients with heart failure," *Neurology*, Vol. 59, No. 4, 2002, pp. 651.
87. Kilander, L., Andren, B., Nyman, H., Lind, L., Boberg, M., and Lithell, H., "Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men," *Stroke*, Vol. 29, No. 9, 1998, pp. 1816-1820.
88. Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., and Bennett, D. A., "Participation in cognitively stimulating activities and risk of incident Alzheimer disease," *JAMA*, Vol. 287, No. 6, 2002, pp. 742-748.
89. Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., Morris, J. N., Rebok, G. W., Smith, D. M., Tennstedt, S. L., Unverzagt, F. W., and Willis, S. L., "Effects of cognitive training interventions with older adults: a randomized controlled trial," *JAMA*, Vol. 288, No. 18, 2002, pp. 2271-2281.
90. Wilson, R. S., Bennett, D. A., Bienias, J. L., Aggarwal, N. T., Mendes De Leon, C. F., Morris, M. C., Schneider, J. A., and Evans, D. A., "Cognitive activity and incident AD in a population-based sample of older persons," *Neurology*, Vol. 59, No. 12, 2002, pp. 1910-1914.
91. Friedland, R. P., Fritsch, T., Smyth, K. A., Koss, E., Lerner, A. J., Chen, C. H., Petot, G. J., and Debanne, S. M., "Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members," *Proc.Natl.Acad Sci U.S.A*, Vol. 98, No. 6, 2001, pp. 3440-3445.
92. Qiu, C., Karp, A., Von Strauss, E., Winblad, B., Fratiglioni, L., and Bellander, T., "Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project," *Am J Ind.Med*, Vol. 43, No. 2, 2003, pp. 204-211.
93. Snowdon, D. A., Greiner, L. H., and Markesbery, W. R., "Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease. Findings from the Nun Study," *Ann N Y.Acad Sci*, Vol. 903, 2000, pp. 34-38.
94. Davis, R. N., Massman, P. J., and Doody, R. S., "Cognitive intervention in Alzheimer disease: a randomized placebo-controlled study," *Alzheimer Dis.Assoc.Disord.*, Vol. 15, No. 1, 2001, pp. 1-9.
95. Gauthier, E., Fortier, I., Courchesne, F., Pepin, P., Mortimer, J., and Gauvreau, D., "Aluminum forms in drinking water and risk of Alzheimer's disease," *Environ.Res.*, Vol. 84, No. 3, 2000, pp. 234-246.
96. Rondeau, V., Commenges, D., Jacqmin-Gadda, H., and Dartigues, J. F., "Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study," *Am J Epidemiol.*, Vol. 152, No. 1, 2000, pp. 59-66.
97. Newman, P. E., "Alzheimer's disease revisited," *Med Hypotheses*, Vol. 54, No. 5, 2000, pp. 774-776.
98. Savory, J. and Garruto, R. M., "Aluminum, tau protein, and Alzheimer's disease: an important link?," *Nutrition*, Vol. 14, No. 3, 1998, pp. 313-314.
99. Mate, G.. When The Body Says No. 2003. New Jarsey, John Wiley and Sons.
100. Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., and Glaser, R., "Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology," *Annu.Rev.Psychol.*, Vol. 53, 2002, pp. 83-107.

101. McGeer, P. L. and McGeer, E. G., "Autotoxicity and Alzheimer disease," *Arch.Neurol.*, Vol. 57, No. 6, 2000, pp. 789-790.
102. Hock, C., Drasch, G., Golombowski, S., Muller-Spahn, F., Willershausen-Zonnchen, B., Schwarz, P., Hock, U., Growdon, J. H., and Nitsch, R. M., "Increased blood mercury levels in patients with Alzheimer's disease," *J Neural Transm.*, Vol. 105, No. 1, 1998, pp. 59-68.
103. Ely, J. T., "Mercury induced Alzheimer's disease: accelerating incidence?," *Bull.Environ.Contam Toxicol.*, Vol. 67, No. 6, 2001, pp. 800-806.
104. Saxe, S. R., Wekstein, M. W., Kryscio, R. J., Henry, R. G., Cornett, C. R., Snowdon, D. A., Grant, F. T., Schmitt, F. A., Donegan, S. J., Wekstein, D. R., Ehmann, W. D., and Markesbery, W. R., "Alzheimer's disease, dental amalgam and mercury," *J Am Dent.Assoc.*, Vol. 130, No. 2, 1999, pp. 191-199.
105. Baldi, I., Lebailly, P., Mohammed-Brahim, B., Letenneur, L., Dartigues, J. F., and Brochard, P., "Neurodegenerative diseases and exposure to pesticides in the elderly," *Am J Epidemiol.*, Vol. 157, No. 5, 2003, pp. 409-414.
106. Hebert, R., Lindsay, J., Verreault, R., Rockwood, K., Hill, G., and Dubois, M. F., "Vascular dementia : incidence and risk factors in the Canadian study of health and aging," *Stroke*, Vol. 31, No. 7, 2000, pp. 1487-1493.
107. Epstein, S. S.. The Politics of Cancer Revisited. 1998. East Ridge Press.
108. Cummings, J. L., "Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations," *Am J Geriatr.Psychiatry*, Vol. 11, No. 2, 2003, pp. 131-145.
109. Sano, M., Ernesto, C., Thomas, R. G., Klauber, M. R., Schafer, K., Grundman, M., Woodbury, P., Growdon, J., Cotman, C. W., Pfeiffer, E., Schneider, L. S., Thal, L. J., and The Members of the Alzheimer's Disease Cooperative Study, "A Controlled Trial of Selegiline, Alpha-Tocopherol, or Both as Treatment for Alzheimer's Disease," *The New England Journal of Medicine*, Vol. 336, No. 17, 1997, pp. 1216-1222.
110. Jiang, Q., Christen, S., Shigenaga, M. K., and Ames, B. N., "gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention," *American Journal of Clinical Nutrition*, Vol. 74, No. 6, 2001, pp. 714-722.
111. Engelhart, M. J., Geerlings, M. I., Ruitenberg, A., van Swieten, J. C., Hofman, A., Witteman, J. C., and Breteler, M. M., "Dietary intake of antioxidants and risk of Alzheimer disease," *JAMA*, Vol. 287, No. 24, 2002, pp. 3223-3229.
112. Grodstein, F., Chen, J., and Willett, W. C., "High-dose antioxidant supplements and cognitive function in community-dwelling elderly women," *American Journal of Clinical Nutrition*, Vol. 77, No. 4, 2003, pp. 975-984.
113. Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., and Wilson, R. S., "Vitamin E and cognitive decline in older persons," *Arch.Neurol.*, Vol. 59, No. 7, 2002, pp. 1125-1132.
114. Ortega, R. M., Requejo, A. M., Lopez-Sobaler, A. M., Andres, P., Navia, B., Perea, J. M., and Robles, F., "Cognitive function in elderly people is influenced by vitamin E status," *J Nutr*, Vol. 132, No. 7, 2002, pp. 2065-2068.
115. Kontush, A., Mann, U., Arlt, S., Ujeyl, A., Luhrs, C., Muller-Thomsen, T., and Beisiegel, U., "Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease," *Free Radic.Biol.Med*, Vol. 31, No. 3, 2001, pp. 345-354.
116. Masaki, K. H., Losonczy, K. G., Izmirlian, G., Foley, D. J., Ross, G. W., Petrovitch, H., Havlik, R., and White, L. R., "Association of vitamin E and C supplement use with cognitive function and dementia in elderly men," *Neurology*, Vol. 54, No. 6, 2000, pp. 1265-1272.
117. Abyad, A., "Prevalence of Vitamin B12 Deficiency Among Demented Patients and Cognitive Recovery with Cobalamin Replacement," *J Nutr Health Aging*, Vol. 6, No. 4, 2002, pp. 254-260.
118. Eastley, R., Wilcock, G. K., and Bucks, R. S., "Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuropsychological function," *Int.J Geriatr.Psychiatry*, Vol. 15, No. 3, 2000, pp. 226-233.
119. Kuzminski, A. M., Del Giacco, E. J., Allen, R. H., Stabler, S. P., and Lindenbaum, J., "Effective treatment of cobalamin deficiency with oral cobalamin," *Blood*, Vol. 92, No. 4, 1998, pp. 1191-1198.
120. Kris-Etherton, P. M., Harris, W. S., and Appel, L. J., "Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association," *Arterioscler.Thromb.Vasc.Biol.*, Vol. 23, No. 2, 2003, pp. 151-152.
121. Kris-Etherton, P. M., Harris, W. S., and Appel, L. J., "Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease," *Arterioscler.Thromb.Vasc.Biol.*, Vol. 23, No. 2, 2003, pp. e20-e30.
122. Sears, B.. The Omega Rx Zone. 2002. New York, Harper-Collins.
123. Hu, F. B. and Willett, W. C., "Optimal diets for prevention of coronary heart disease," *JAMA*, Vol. 288, No. 20, 2002, pp. 2569-2578.
124. Yehuda, S., Rabinovtz, S., Carasso, R. L., and Mostofsky, D. I., "Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life," *Int.J Neurosci.*, Vol. 87, No. 3-4, 1996, pp. 141-149.

125. Terano, T., Fujishiro, S., Ban, T., Yamamoto, K., Tanaka, T., Noguchi, Y., Tamura, Y., Yazawa, K., and Hirayama, T., "Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases," *Lipids*, Vol. 34 Suppl, 1999, pp. S345-S346.
126. Peers, R. J., "Alzheimer's disease and omega-3 fatty acids: hypothesis," *Med J Aust.*, Vol. 153, No. 9, 1990, pp. 563-564.
127. Birks, J., Grimley, E. V., and Van Dongen, M., "Ginkgo biloba for cognitive impairment and dementia," *Cochrane.Database.Syst.Rev.*, No. 4, 2002, pp. CD003120.
128. Andrieu, S., Gillette, S., Amouyal, K., Nourhashemi, F., Reynish, E., Ousset, P. J., Albarede, J. L., Vellas, B., and Grandjean, H., "Association of Alzheimer's disease onset with ginkgo biloba and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study," *J Gerontol.A Biol.Sci Med Sci*, Vol. 58, No. 4, 2003, pp. 372-377.
129. Solomon, P. R., Adams, F., Silver, A., Zimmer, J., and DeVeaux, R., "Ginkgo for memory enhancement: a randomized controlled trial," *JAMA*, Vol. 288, No. 7, 2002, pp. 835-840.
130. Nathan, P. J., Harrison, B. J., and Bartholomeusz, C., "Ginkgo and memory," *JAMA*, Vol. 289, No. 5, 2003, pp. 546-548.
131. Luo, Y., Smith, J. V., Paramasivam, V., Burdick, A., Curry, K. J., Buford, J. P., Khan, I., Netzer, W. J., Xu, H., and Butko, P., "Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761," *Proc.Natl.Acad Sci U.S.A*, Vol. 99, No. 19, 2002, pp. 12197-12202.
132. Fassbender, K., Masters, C., and Beyreuther, K., "Alzheimer's disease: an inflammatory disease?," *Neurobiol.Aging*, Vol. 21, No. 3, 2000, pp. 433-436.
133. Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L., Finch, C. E., Frautschy, S., Griffin, W. S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I. R., McGeer, P. L., O'Banion, M. K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F. L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G., and Wyss-Coray, T., "Inflammation and Alzheimer's disease," *Neurobiol.Aging*, Vol. 21, No. 3, 2000, pp. 383-421.
134. McGeer, P. L., Schulzer, M., and McGeer, E. G., "Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies," *Neurology*, Vol. 47, No. 2, 1996, pp. 425-432.
135. Zandi, P. P. and Breitner, J. C., "Do NSAIDs prevent Alzheimer's disease? And, if so, why? The epidemiological evidence," *Neurobiol.Aging*, Vol. 22, No. 6, 2001, pp. 811-817.
136. Launer, L., "Nonsteroidal anti-inflammatory drug use and the risk for Alzheimer's disease : dissecting the epidemiological evidence," *Drugs*, Vol. 63, No. 8, 2003, pp. 731-739.
137. Shumaker, S. A., Legault, C., Thal, L., Wallace, R. B., Ockene, J. K., Hendrix, S. L., Jones, B. N., III, Assaf, A. R., Jackson, R. D., Morley, K. J., Wassertheil-Smoller, S., and Wactawski-Wende, J., "Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial," *JAMA*, Vol. 289, No. 20, 2003, pp. 2651-2662.
138. Rapp, S. R., Espeland, M. A., Shumaker, S. A., Henderson, V. W., Brunner, R. L., Manson, J. E., Gass, M. L., Stefanick, M. L., Lane, D. S., Hays, J., Johnson, K. C., Coker, L. H., Dailey, M., and Bowen, D., "Effect of Estrogen Plus Progestin on Global Cognitive Function in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial," *JAMA*, Vol. 289, No. 20, 2003, pp. 2663-2672.
139. Banaclocha, M. M., "Therapeutic potential of N-acetylcysteine in age-related mitochondrial neurodegenerative diseases," *Med Hypotheses*, Vol. 56, No. 4, 2001, pp. 472-477.
140. Atkins, R. C.. Dr. Atkins' Vita-Nutrient Solution. 1998. New York, Simon and Schuster.
141. Packer, L.. The Antioxidant Miracle. 1999. New York, John Wiley & Sons.
142. Hager, K., Marahrens, A., Kenklies, M., Riederer, P., and Munch, G., "Alpha-lipoic acid as a new treatment option for Azheimer type dementia," *Arch.Gerontol.Geriatr.*, Vol. 32, No. 3, 2001, pp. 275-282.
143. Berkson, B.. The Alpha Lipoic Acid Breakthrough. 1998. California, Prima Communications.
144. Pope, S. K., Shue, V. M., and Beck, C., "Will a healthy lifestyle help prevent alzheimer's disease?," *Annu.Rev.Public Health*, Vol. 24, 2003, pp. 111-132.
145. Chertkow, H., "Mild cognitive impairment," *Curr.Opin.Neurol.*, Vol. 15, No. 4, 2002, pp. 401-407.
146. Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., Ritchie, K., Rossor, M., Thal, L., and Winblad, B., "Current concepts in mild cognitive impairment," *Arch.Neurol.*, Vol. 58, No. 12, 2001, pp. 1985-1992.
147. Prasad, K. N., Cole, W. C., Hovland, A. R., Prasad, K. C., Nahreini, P., Kumar, B., Edwards-Prasad, J., and Andreatta, C. P., "Multiple antioxidants in the prevention and treatment of neurodegenerative disease: analysis of biologic rationale," *Curr.Opin.Neurol.*, Vol. 12, No. 6, 1999, pp. 761-770.

# Stress and Allergies

## by Thomas Ogren

**Wisdom from the Vet**

When I was in college I took a class in veterinary science that was given by the head veterinarian of the university, Dr. Dale Smith. Our university was known for its school of agriculture and had a reputation as being a "hands on" college. As a result we had large herds of cattle, flocks of sheep, pigs, horses, fowl and so forth. Our vet believed in a holistic approach to animal health.

Dr. Smith had been the university vet for almost thirty years, and his own father had been a vet before him. The first day he told our class, "The most important thing of all for you to be concerned with in animal health is reducing stress. Virtually all the diseases of livestock you will encounter are caused by stress. " He further explained that most genetic diseases had long ago been eliminated with livestock through selective breeding. What you saw instead were animals that were sick because the farmer or rancher wasn't taking care of them properly. They were left outside with no shade in the heat, left with no protection to get out of the wind, stuck in an over-crowded corral, fed a diet too low in nutrients, something that would cause stress. "The stress causes a breakdown," said the vet, "and then disease of some kind shows up. It could be a pneumonia, cancer, allergies, any number of things, but stress always sets the stage for the disease."

I have long wondered how it was that a veterinarian understood this so clearly and our own doctors didn't seem to pay much attention to it at all. We are animals after all. Stress must affect us just as it does all the other species of animals. I think most of us who have lived with allergies understand that stress can aggravate the allergies. We'll never be able to eliminate all stress from our lives. But we can learn ways to reduce it, and we can learn ways to deal with it. Whenever possible it is healthy to try to see some of this stress as a challenge. If we live active lives, we can expect plenty of stress, and that's all right as long as we don't let it get the best of us.

In my books, *Allergy-Free Gardening* and *Safe Sex in the Garden,* I explore how plant sex influences human wellness. If we have female rather than male plants, we won't be inhaling all that male pollen and we won't suffer from it. Allergy-friendly yards and gardens are stress busters.

In addition to decreasing the number of allergens, pollen grains, molds, and fungal spores, there are other things we can do to reduce stress in our lives, in our gardens.

**Are allergies just a head-trip?**

There is a reoccurring problem with stress and allergies. The problem is one of perception. It is well known that stress aggravates allergies. If you did a computer search using the terms "stress, illness, disease," you might well be amazed at the hundreds of thousands of entries you'd find. For example, on the website healthdoc.com there's an article, "Stress, the Number One Cause of Disease and Illness." Even if the role of stress and illness is not as generally well understood, as it ought to be, it is certainly well documented. Stress contributes to heart disease in certain individuals. Stress also contributes to high blood pressure, high cholesterol, and other cardiac risk factors, and many other negative things as well. Someone with allergies who is under stress will almost certainly experience worse allergies. The problem here is that too many people mix up cause and effect. Allergies are caused by an allergic response to allergens, to perfectly real substances, pollens, molds, dust, dander, allergic plant saps and so forth.

All too often ignorant people will imply that someone has allergies simply because they don't know how to deal with stress. The implication is that you have allergies because you don't really have your head screwed on straight. This isn't true at all, and actually it is rather insulting. The next step in this illogical progression is that you deserve to have allergies since you're bringing it on yourself. The people making these assumptions are, of course, people who don't have allergies themselves. They don't know how lucky they are, nor do they realize how arrogant are their views. Having persistent allergies can become pretty depressing and frustrating and critics are often insensitive to this as well.

Yes, allergies can be aggravated by stress, but then too, so can any other illness be complicated by stress. Allergies are completely for real. A few examples of this: Years ago when I gave my students different flowers to sniff, we quickly found out that a third of the class reacted strongly to bottlebrush pollen. Later, in blind tests with different types of pollen, the same students all again reacted strongly to the bottlebrush pollen. Another example: I have seen people who were very allergic to shrimp. I have seen what happened to them when they ate some food that they'd been told did not have shrimp in it, but that actually did. They immediately became very ill.

When an allergist skin tests someone, often this is done on their back. They can't see the pricks nor do they know which allergen is being tested with each prick of the skin. Their skin will then react with a welt to the ones they are allergic to. If they are re-tested soon afterwards, the results will be the same. Allergic responses are totally for real and this simple fact needs to be respected. Back to stress. Here are some things we can do to reduce stress in our gardens.

**Forget about perfection**
We don't need perfect gardens, not at all. Our gardens do not need to conform to some ideal. We should have gardens that please us, and that is what's really important. Think of your garden as your place to feel relaxed, to kick back, to unwind. Good gardens can be great stress reducers.

**Garden design**
When you first set up your gardens think about how they will be used. Borrow liberally from good feng shui concepts of energy and harmony. Consider first the function and design gardens that are a pleasure to be in. If you can possibly afford it, get professional advice from a landscape designer or a landscape architect. These people are experts on how to create comfortable, attractive, stress-free gardens. Their advice might, in the long run, turn out to be quite a bargain. With some things you do get what you pay for. With a good designer you get a quality design, one that will long keep you pleased.

While you're thinking about how your landscape might look, buy some of the magazines on landscape design and look them over. See what attracts you. There are many excellent books on landscape design and these too can help you set up a relaxing, enjoyable garden. I recommend you go down to the bookstore, take some time, and look over all the books on garden design. Even if your yards are already landscaped, these books and magazines are still valuable, because you can always make changes. You can always try to improve your garden.

**Wild birds**
Wild birds in a garden make it more fun and it is stress reducing just to watch them. All bird feeders add to your pleasure. I especially love those long, porous mesh bags that you can fill with Niger thistle seed. You hang these over a high branch, and the goldfinches will go crazy for it. Quickly the little goldfinches become almost tame. Just watching them feed is relaxing. The larger, more aggressive sparrows tire quickly of trying to feed from these mesh bags, and this conserves the Niger seed, which as bird seed goes, is a bit pricey. Humming bird feeders are great additions to a garden and who doesn't like to watch humming birds? If you can't appreciate humming birds, almost certainly your life has far too much stress in it right now. Hang up a hummingbird feeder, relax, and enjoy the show. A birdbath can be handsome in the garden, and the birds will enjoy it too. Watching robins splash in a birdbath is good karma. Be sure to keep the water clean. A dirty birdbath can spread diseases among the birds, so hosing it out daily is a great idea.

**Wind chimes**
I especially like those bamboo wind chimes but actually, almost any wind chimes add a nice, mellow touch in the garden. I will admit though that there are a few chimes that are pitched too high for my taste. The most important thing is that the chimes sound pleasant to you. Hang your chimes in a spot free of obstructions, where they will catch the breeze. When the wind blows, the chimes sing to you.

**Water**
Little ponds, tiny waterfalls, water fountains, all of these are proven stress reducers. Certain sounds irritate the human psyche, car alarms blasting in the night, dogs barking on and on. But other sounds soothe the soul like the sound of splashing water or water tumbling over stones. Placed in the right spot in a garden all

these wet additions can do much for the ambiance of the landscape. Fish in a pond can add quite a bit too. More than one new parent has discovered the calming effect that watching fish swim in an aquarium has on their babies. A few goldfish in a pond is attractive too. A little pond also expands the kinds of plants you can grow in your garden. With a pond you can have water lilies. Today there are many water fountains available and some are not too expensive either. Considering their value for reducing stress, they seem like a bargain.

**Lawn furniture**
This needn't be anything fancy, but every garden ought to have a nice spot or two to sit and relax. A few garden chairs can make a big difference. A little table is good too. Lounge chairs are by design stress-busters. When I was young we had something called a chaise lounge that rocked and was just plain fun to sit in. More stress reduction. If you have an overhanging branch that looks perfect for it, hang a swing from it. Swinging reduces stress too. There has been considerable research into the importance of rocking babies back and forth. Any mother understands how well this works. Perhaps swinging works the same way? A comfortable garden bench is a worthy addition to any landscape. Place it where two lovers, young or old, can sit and enjoy the view and each other.

**Read a book**
Seriously, sit in an easy chair in your comfortable garden and read a book. Turn off the TV and go outside. Commune with Nature. Read a book on how to reduce stress in your life if you think it might help. Read something on how to maintain a positive, cheery attitude. I find these always give me a boost. But just sitting in the garden and reading a good book is stress reducing. The natural light is good for your eyes and good for all of you. Read a novel if you like. Do sit out in your garden and read. The results are all positive.

**Fruit trees**
Why not use some fruit trees in the landscape? There is something so basic, so fundamentally satisfying to go outside on a warm summer morning and pick a ripe apricot, peach, apple, or plum. Actually, just watching the fruit develop on the tree is satisfying too. If you're inclined and you turn some of that fruit into jams, jellies, pies, or preserves, that's also fantastic. And fruit trees can be perfectly ornamental in the landscape. Few trees look half as good to me as a fruit laden apricot tree.

**Vegetables**
If you have the space consider some kind of a vegetable garden too. There is something about growing tomatoes and string beans that is good for the soul. You certainly don't need a large spot for growing vegetables although it would be great if you had the room. Working in a vegetable garden is relaxing, something very basic. If you have a spot that gets good sunlight most of the day, consider having some sort of a vegetable garden. Even if it is just a little area where you can grow a few tomato plants each year, the pleasure and stress reduction from this can be incredible.

**Compost**
A compost pile doesn't need to be big or fancy or complicated. You can build a simple wooden box with no bottom and throw all your old banana peels, apple cores, carrot tops, grass clippings, leaves and so on into it. Get some red worms and add them to the compost. They'll multiply like mad and turn all the garbage into wonderful compost. Now and then you can remove some of the finished compost and use it in you garden. Composting is easy, fun, is earth-friendly, and it makes you feel good.

**A Barbecue**
It doesn't need to be elaborate but if you still enjoy a hamburger or steak or grilled piece of chicken, why not have some kind of a barbecue? Even if you're vegetarian, you can still cook outside on a grill. Bell peppers, chilies, and corn taste great right off a grill. Anyhow, you can get creative. Sometimes this provides a good excuse to sit out in the yard while the food cooks. A barbecue can turn an ordinary meal into a little outdoor adventure.

**Moveable Pots**
I like to have some large pots of flowers that I move around. When they are looking great, I move them up front where everyone can see them. When they are looking ratty, I stick them off on the side of the house to

recuperate. I use enough moveable pots with enough different kinds of flowers planted in them, so that I can almost always have something colourful to brighten up any day.

**A Lawn**
Lawns are a lot of trouble supposedly but really, they are great places for kids to play on. Far too many people get hung up on having a "perfect lawn" and with this attitude a lawn can quickly become a big chore. A perfect lawn ought to be a lawn that you like. If it has three different kinds of grasses in it and a dandelion or two---and that doesn't bother you, then that's a great lawn. Lawns don't need to be huge; in fact excessively large lawns are not worth the effort. But a small nice piece of lawn is a people-friendly addition to a garden. Use lawn grasses that are low-pollen or pollen-free.

**Privacy**
If you like to sunbathe in the nude or just feel like walking out back in your underwear in the morning, you ought to be able to do it without some neighbor looking at you. Front yards can be wide open perhaps, but a back yard needs to provide some privacy. Screens of shrubs or trees can provide this as can a simple 6-foot tall cedar board fence. Having privacy in your garden makes it feel like more of a retreat, a spot to get away from the troubles of the world, somewhere to step right out of the rat race.

*The author, Thomas Leo Ogren, is an internationally recognized expert on plant sexuality as it relates to human health. He is author of Allergy-Free Gardening, and also of Safe Sex in the Garden. His work has been reviewed in many publications including Alternative Medicine, Garden Design, Women's Day, Earth Island Journal, Wild One's Journal, New Scientist, Landscape Design, Pacific Horticulture, the London Times, and Garden Gate. He has made numerous appearances on HGTV and was the focus of a recent Discovery Channel episode. He does consulting work for county asthma coalitions, the USDA, and the American Lung Association.*
*Contact Tom through his website: http://www.allergyfree-gardening.com/welcome.php*

INTERNATIONAL HEALTH NEWS is published 10 times a year by:
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5

E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com
ISSN 1203-1933 