Age-related Cognitive Dysfunction (Dementia): A Natural Approach

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INTRODUCTION

The term "age-related cognitive dysfunction" can refer to a number of disorders from the relatively common age-related memory impairment, to progressive dementias such as Alzheimer's disease. According to the World Health Organization:

> *Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple cortical functions, calculation, learning capacity, language and judgment. Impairments of cognitive function are commonly accompanied, and occasionally preceded by deterioration in emotional control, social behavior, or motivation* (Jacques & Jackson 2000:2).

This review will focus on the dementias. The first part will examine their types, prevalence, etiology, and impact on family. The second part will discuss nutritional guidelines for older adults, dietary supplements that may have benefit for dementia, and natural protocols for individual types of dementia.

PART 1

Although there are many types and of dementia (table 1), the most prevalent types of dementia include Alzheimer's disease, vascular dementia and Parkinson's disease (Spence 1999). These are the dementias that will be addressed in this review.

Each type of dementia might be experienced in different degrees. Spence (1999) has indicated that 10% of the total population under 65 years of age is affected by mild dementia and that only 5% of that age group suffers from severe dementia. By contrast, about 15% of those over 85 years of age have severe dementia, and its prevalence is predicted to double over the next 60 years.

TABLE 1 – DEMENTIA: TYPE, CAUSES & TREATMENTS

Type	Cause	Conventional Treatment
Dementia of Alzheimer type (DAT)	Plaques, tangles, transmitter defects, abnormal amyloid deposition	Anticholinesterases, nerve growth Factor
Vascular dementia	Multiple infarcts, stroke, small vessel disease	Aspirin, lower blood pressure, lower cholesterol
Lewy body dementia	Lewy bodies, transmitter defects	Anticholinesterases
Parkinson's disease	Lewy bodies especially in basal Ganglia	Antiparkinsonian drugs do not help Dementia
Frontal lobe dementia	Various, including Pick's	
Normal pressure hydrocephalus	Obstructed cerebrospinal fluid flow due to previous damage, e.g. subarachnoid hemorrhage, meningitis	Surgery (shunt)
Punch-drunk syndrome	Repeated head injury	Stop the damage
Slow-growing brain tumor	Pressure causes destruction of brain	Surgery
Aluminum and other metals	Direct toxic effect	Remove the poison

Wilson's disease	Toxicity of copper	Penicillamine
Alcohol abuse	Toxic effect and thiamine deficiency	Abstinence, thiamine treatment
Huntington's chorea	Genetic abnormality	Screening available
Syphilis (GPI)	Infective	Antibiotics
AIDS	Infective, secondary infection	Anti-AIDS drugs
Vitamin (e.g. B12) deficiencies	Toxic?	Replacement
Hypothyroidism	Toxic?	Replacement
Parathyroid disorders	Calcium metabolism altered	Medical or Surgical
Adapted from *Jacques, A. & Jackson, G.A. 2000, Understanding Dementia, 2nd ed, Churchill Livingstone, Edinburgh.*		

Alzheimer's disease

Although dementia of the Alzheimer's type (DAT) is the correct name for this dysfunction, it is popularly known as Alzheimer's disease. This is the most common form of dementia, affecting 50-60% of geriatric patients who have dementia. Over the age of 65, one person in 10 can be expected to be afflicted with DAT. This ratio increases to 4 in 10 in those over 85 (Spence 1999).

According the the Alzheimer's Association (2006), "Alzheimer's (*AHLZ-high-merz*) disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer's progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations."

In this dysfunction, the areas of the brain that control memory and thinking skills are affected first, but as the disease progresses, cells die in other regions of the brain. Eventually, the person with Alzheimer's will need complete care. If the individual has no other serious illness, the loss of brain function itself will cause death (Alzheimer's Association 2004).

In DAT, the cerebral hemispheres shrink and lose weight; an indication of cell death. Even more significant is widespread evidence of neuronal (i.e., nerve cell) degeneration, particularly their endings and connections (axons and dendrites) (Jacques & Jackson 2000). Neurofibrillary tangles and neuritic plaques appear to contribute to this problem (Spence 1999; Jacques & Jackson 2000).

There is some evidence that there is a genetic predisposition to DAT. This may, at least in part, be a function of apolipoprotein E (ApoE) which is involved in the transport and metabolism of fats. ApoE is found in three major forms in the membranes of neurons: ApoE2, ApoE3 and ApoE4. These forms are inherited; and if you inherit two ApoE4 (one from each parent), you are at greater risk for DAT and vascular dementia (Jacques & Jackson 2000)

There is also evidence, although not conclusive, that aluminum may be involved in the genesis of DAT. Patients receiving renal dialysis had a higher incidence of DAT due to the concentration of aluminum in the water (this has changed now with the use of specific dialysis fluids). Rabbits fed large amounts of aluminum were found to develop tangles similar to those found in patients with DAT. Also, a high concentration of aluminum was thought to be found in the plaques of DAT patients. However, there is no evidence of increased incidence of DAT in areas with high aluminum in the water (Jacques & Jackson 2000).

Also, the concentration of free radicals has been shown to increase with age, and this has also been implicated in the development of DAT.

Vascular dementia
Next to DAT, vascular dementia (VaD) is most common, accounting for 20-30% of all dementias. VaD is primarily a disease of the arteries, and patients typically show evidence of vascular disease in other areas of the body; such as heart disease, poor circulation to the legs, or high blood pressure. There are different types of VaD, with the most common type being multi-infarction dementia (Spence 1999; Jacques & Jackson 2000).

Basically, multi-infarction dementia this is caused by atherosclerosis of blood vessels leading to the brain with periods of decreased blood flow, resulting in repeated ministrokes in regions of the brain. The ministrokes cause cells to die, producing deteriorated areas called infarcts. If the ministrokes continue, the person may begin to show symptoms similar to those of DAT (Spence 1999). Absentmindedness can also be an early symptom of brain damage and VaD, although just because you are absentminded doesn't necessarily mean you have VaD.

The causes and risk factors for VaD can generally be the same for vascular disease in general: high levels of serum cholesterol and triglycerides, high levels of homocysteine and C-reactive protein, smoking, etc. Other research has shown that people with VaD also seem to have had exposure to higher levels of fibrinogen (clotting factor) over a long period of time (Alzheimer's Society 2006.)

Parkinson disease
According the National Parkinson Foundation (2006), the United States is estimated to have 60,000 newly diagnosed cases of Parkinson disease (PD) diagnosed each year, joining the 1.5 million Americans who currently have PD. While the condition usually develops after the age of 65, 15% of those diagnosed are under 50. Since about 20% of patients develop DAT, PD is considered to be a type of dementia (Spence 1999).

The actual cause of this brain disorder is unknown. It occurs when certain neurons in a part of the brain called the substantia nigra die or become impaired. Normally, these cells produce the neurotransmitter dopamine. Dopamine allows smooth, coordinated function of the body's muscles and movement. When approximately 80% of the dopamine-producing cells are damaged, the symptoms of PD appear. These include tremor (shaking), slowness of movement, rigidity (stiffness), and difficulty with balance; and may also include small, cramped handwriting, stiff facial expression, shuffling walk, muffled speech and depression (National Parkinson Foundation 2006).

In PD, dopamine is unable to cross the blood-brain barrier, which regulates the exchange of substances between the cells of the brain and the cerebral blood vessels. Therefore, the administration of dopamine is not an affective treatment. The administration of L-dopa, however, which is a precursor to dopamine, can help reduce muscle rigidity and tremors, and improve posture and speech (Spence 1999).

Impact of dementia care on the family
In a community setting, families bear the major responsibility as caretakers for dementia patients (Wijeratne 1997). The role of family in dementia care varies with specific families, the individual personalities involved, and how families react and cope with the dementia sufferer (Jacques & Jackson 2000). These factors can play a significant role in outcomes, both for the sufferer and the caregivers.

In dementia care, the role of family may be function of individual reactions and attitudes towards the sufferer's current stage of dementia, as well as other factors. Jacques & Jackson (2000) categorized and described family reactions to dementia as 1) the dying relationship, 2) the changing relationship, and 3) the continuing relationship.

The dying relationship

Due to the decline in personality, self-care and intellect, dementia has been described as living death. Family members often experience feelings of loss (similar to grief), and go through the phases of grief related to death (Jacques & Jackson 2000). It is not unusual for caregivers to experience varying degrees of depression. As a matter of fact, the caregivers' depression can be correlated with certain predictors. In a study by Fuh et al. (1999), twenty-six (about 35%) of seventy-four caregivers were classified as depressed. The depression scores of the caregivers were positively correlated with frequency of using coping strategies to manage distress as well as frequency of the patients' disruptive behavior, and were correlated negatively with the educational years of the caregivers.

The changing relationship

The relationship between family and sufferer tends to change as the family comes to terms with the dementia sufferer's decline. The change is primarily characterized by the sufferer's shift to dependence upon the family, or a key family member or members. This shift is gradual (Jacques & Jackson 2000:238-245), although the caregiver's sense of burden is variable. It not only involves the stressors of dementia itself, but also developmental and cultural factors, as well as 'carer's gender, coping style, social network, and the carer's level of intimacy with the elder' (Wijeratne 1997).

An important consideration in the changing relationship is the caregivers' state of mental and physical health, and its potential to change. In a journal review, Wijeratne (1997) found that caregivers seem to suffer from at least moderate levels of psychological symptoms, and they tend to judge their own health to be poorer than that of controls. In the same review, Wijeratne also indicated that 'Caregiving in dementia appears to be at least as stressful as that in chronic physical illness and depression.'

The continuing relationship

Providing care for a family member suffering from dementia is heavy task, often associated with varying degrees of difficulty, stress and burden. Despite this, family caregivers frequently chose to continue their relationship until the end of the sufferer's life (Jacques & Jackson 2000:257). Such a choice may help fulfill the caregiver's sense of filial duty, and in some cases may allow couples to maintain an affectionate relationship well into dementia (Jacques & Jackson 2000:257).

The continuing relationship will likely require some outside help. Such help should be introduced gradually and sensitively (Jacques & Jackson 2000:257).

Another positive outcome from the continuing relationship may be raising a child with a greater sense of empathy and caring. In a study conducted by Beach (1997), twenty adolescents aged 14-18 were interviewed regarding their sense of satisfaction related to their experience in caregiving in the immediate family for a parent, grandparent, aunt or uncle suffering from Alzheimer's Type Dementia. The results indicated that there was increased sibling activity/sharing, greater empathy for older adults, significant mother-adolescent bonding, and peer relationship selection and maintenance.

Carer support agencies

In the United States, there are a few national agencies that offer caregiver support. One such agency is Family Caregiver Alliance (FCA). FCA is a community-based nonprofit organization that addresses the needs of families and friends providing long-term care at home. According to their website (Family Caregiver Alliance 2004), "FCA now offers programs at national, state and local levels to support and sustain caregivers." These programs include information (e.g., publications including fact sheets, newsletters, research studies, reports, policy briefs and other materials), education and training (e.g., caregiver workshops, state-of-the-art research presentations, professional training and public policy conferences), online services and other services.

The Department of Health and Human Services offers the National Family Caregiver Support Program (NFCSP). In addition to a variety of services, the NFCSP website (National Family Caregiver Support Program 2004) provides a link to state and local organizations on aging that can assist caregivers in caring for their loved ones; including resources on finding a local support group.

The Alzheimer's Association (2004) is a national voluntary health organization supporting Alzheimer's research and care. This organization provides information about Alzheimer's disease, programs, services, and advocacy. This includes finding local chapters, safety services (assists in the safe, timely return of individuals with Alzheimer's disease and related dementias who wander off and become lost), information services (online and library), and a 'Partnering with Your Doctor' workshop for caregivers.

Other caregiver support agencies include:

- The National Family Caregivers Association (2004) is a caregiver membership organization that provides services in the areas of information and education, support, public awareness and advocacy for caregivers.

- The National Respite Locator Service (2004) is an organization that helps parents, caregivers, and professionals with disabilities, those with chronic or terminal illness, or children at risk for neglect and abuse find respite services in their state and local area.

PART 2

Currently, there are a variety of drugs used to treat dementia patients including anti-dementia agents, hypnotic anxiolytics, antidepressants and neuropletics (Jacques & Jackson 2000). These drugs are not without side effects, and polypharmacy can increase the risk of side effects (such as delirium) (Jacques & Jackson 2000). Hence, the benefit-to-risk profiles of such drugs need to be carefully considered when attempting to achieve a balance between adverse reactions/drug interactions and clinically relevant results. To this end, complementary/integrative practitioners may consider the use of nutritional and botanical therapies which have proven degrees of efficacy and generally favorable benefit-to-risk profiles in the treatment of dementias and other severe cognitive dysfunction (Kidd 1999). As a nutritionist and medical herbalist, this is the approach I take (along with dietary modification) as part of a holistic team program for dementia therapy.

The format for Part 2 is as follows. First I will begin be reviewing general dietary and nutritional guidelines for older adults. As always, proper nutrition should be addressed prior to beginning a dietary supplement program. Next I will examine research on individual dietary supplements

that may have value in dementia. Finally, I will propose individual protocols for different types of dementia.

Dietary and nutritional guidelines for older adults

Knowledge about the nutritional needs of older people has advanced within the last 10-15 years. In 1989, the United States Recommended Dietary Allowance (RDA) continued to combine all people over 50 into a single group. The 1997 revision of Dietary Reference Intakes (RDI), however, split this group in two age categories (at least as far as micronutrients are concerned): individuals from 51 to 70 years of age, and individuals 71 and over (Whitney et al. 1998). Considering that persons over age 65 made up 12 percent of the population (Gerrior 1999), and since estimates are that one in five Americans will be 65 or older by the year 2050, and the fastest growing segments of the population include those people aged 85 years and older (McGee & Jensen 2000), the need for these age-specific nutritional requirements are evident. The new RDI for older people are represented in the following table (adapted from Dietary Reference Intakes 1998):

Dietary Reference Intakes (RDIs)

Life-Stage Group	Calcium (mg/d)	Phosphorus (mg/d)	Magnesium (mg/d)	Vitamin D[bc] (µg/d)	Fluoride (mg/d)	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin[d] (mg/d)	Vitamin B-6 (mg/d)	Folate[e] (µg/d)	Vitamin B-12 (µg/d)	Pantothenic Acid (mg/d)	Biotin (µg/d)	Choline[f] (mg/d)
Males														
31-50 y	1,000	700	420	5	4	1.2	1.3	16	1.3	400	2.4	5	30	550
51-70 y	1,200	700	420	10	4	1.2	1.3	16	1.7	400	2.4 (g)	5	30	550
> 70 y	1,200	700	420	15	4	1.2	1.3	16	1.7	400	2.4 (g)	5	30	550
Females														
31-50 y	1,000	700	320	5	3	1.1	1.1	14	1.3	400 (h)	2.4	5	30	425
51-70 y	1,200	700	320	10	3	1.1	1.1	14	1.5	400	2.4 (g)	5	30	425
> 70 y	1,200	700	320	15	3	1.1	1.1	14	1.5	400	2.4 (g)	5	30	425
19-30 y	1,000	700	310	5	3	1.5	1.6	17	2.0	500	2.8	7	35	550
31-50 y	1,000	700	320	5	3	1.5	1.6	17	2.0	500	2.8	7	35	550

This RDI table only represents the micronutrients, since the RDA for energy and protein remained the same; specifically a reduction in kcal and the same grams of protein compared to the previous age groups (adapted from Whitney et al. 1998):

	Energy (kcal)	Protein
Males 25-50	2900	63
Males 51+	2300	63
Females 25-50	2200	50
Females 51+	1900	50

Energy requirements

Such a decrease in energy is appropriate since basal energy requirements decrease with advancing age. This reduction in energy need is due primarily to a decrease in lean muscle mass and metabolic rate (Chernoff R. 2003). Yet, there are varying opinions with regard to the appropriate levels of energy and macronutrient intake, some of which are at variance with RDA levels. According to Meyyazhagan and Palmer (2002), the following simple guidelines can be used to estimate nutritional requirements for total maintenance energy requirement for very old adults (undefined by authors):

1. Low stress: 20 kcal/kg/day
2. Moderate stress: 25–30 kcal/ kg/day
3. Severe stress: 35 kcal/kg/day

Carbohydrates

Carbohydrates should comprise about 55% to 60% of total energy intake (Meyyazhagan & Palmer 2002) with whole grain and complex carbohydrate rich in fibers foods being emphasized (Chernoff R. 2003). However, Stechmiller (2003) has indicated that older adult usually do not consume the recommended 30 kcal/kg/day for energy needs.

Protein

With the decline in energy intake, Meyyazhagan and Palmer (2002) proposed that the protein RDA should be increased from 0.8 g/kg/day to at least 1 g/kg/day (and further increased to 1.2 to 1.5 g/kg/day in periods of stress to offset a negative nitrogen balance). Likewise, Stechmiller (2003) has indicated that older adults may have increased protein requirements over younger adults, and recommends 1.0 g/kg/day for nonstressed, healthy older adults to maintain a positive nitrogen balance. This increase in protein requirements may, in part, be a function of the common loss of muscle mass associated with aging (British Nutrition Foundation 1996). At these levels, protein would represent 10% to 20% of total energy intake.

Fat

Although some controversy exists regarding fat requirements in older adults, it is clear that fat provides a concentrated source of calories, essential fatty acids, and some fat-soluble vitamins (Stechmiller 2003). General dietary recommendations (Whitney et al. 1998) are that optimal diet should contain 30% or less of fat, with 10% polyunsaturated fatty acids, 10% to 15% monounsaturated fat, and less than 10% saturated fat. Meyyazhagan and Palmer (2002) have indicated that in undernourished patients, however, higher quantities of dietary fat (calorie-dense foods) are warranted.

Fluid intake

Maintaining adequate fluid intake is also an important nutritional consideration, and sometimes problematic since the sensation of thirst is often disturbed in older people (British Nutrition Foundation 1996). Three standard guidelines for appropriate fluid intake are (Stechmiller 2003):

1. 30 mL/kg body weight

2. 1 mL/kcal/energy consumed
3. 100 mL/kg, 50 mL/kg for the next 10 kg, and 25 mL/kg for the remaining kg

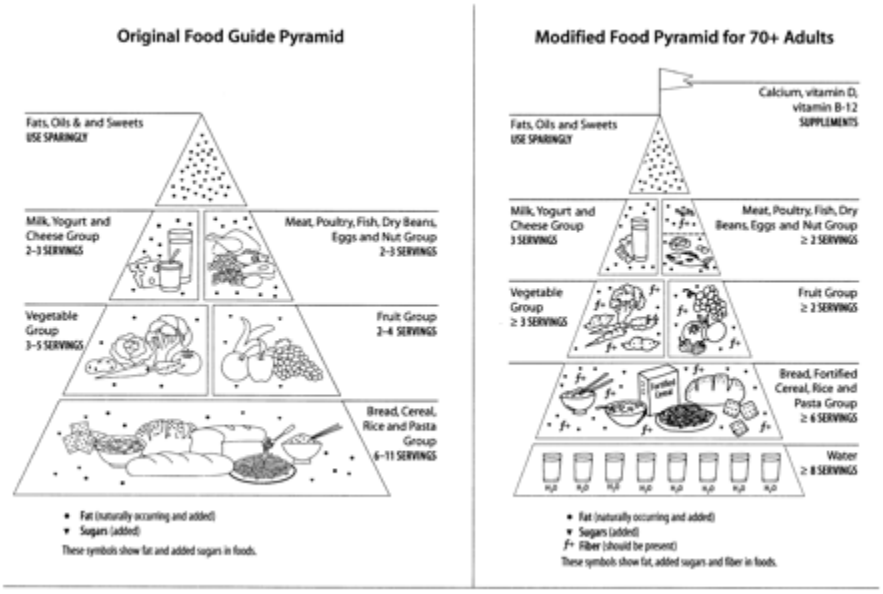
McGee et al. (1999:1022-1029) gives 1500 to 2000 mL of fluid per day as a general recommendation for institutionalized adults.

Micronutrients

The previous RDI table provided a listing vitamin and mineral recommendations for older adults. However, fifty percent of older adults fail to meet these recommendations, and 10% to 30% have subnormal levels of vitamins and minerals (Johnson et al. 2002). Given the reduction in energy intake (Chernoff R. 2003:12-20), this is not entirely surprising. According to Stechmiller (2003), when caloric intake falls below 1500 kcal/day, mineral and vitamin deficiencies are likely. For this reason, researchers (Fletcher & Fairfield 2002) have recommended that the elderly consider a dose of two multiple vitamins daily; or one multiple vitamin with additional supplements of vitamin B12 and D. Other researchers (Johnson et al. 2002; McClain et al. 2002) have made similar recommendations. Considering that the malabsorption of dietary carbohydrates, lipids, amino acids, minerals and vitamins has been documented in the elderly (Woudstra & Thomson 2002), these recommendations for the use of dietary supplements take on even greater significance.

Modified Food Pyramid for 70+ Adults

Due to the fact that people above 70 years old are particularly vulnerable to compromised nutrient intake resulting from decreased energy needs decrease and a decrease in food intake, researchers (Russell et al. 1999) developed the 'Modified Food Pyramid for 70+ Adults' (see figure below). According to Russell et al. (1999), this modified Food Guide Pyramid highlights specific selections within each food group category in order to emphasize foods with a high ratio of nutrients to energy to help ensure adequate nutrient intakes. The Pyramid is also narrowed to reflect lowered energy needs. The new Pyramid includes a small supplement flag at the top and symbols for water and fiber. The supplement flag is included since it is very hard for a person above the age of 70 to obtain adequate intakes of particular nutrients due to the reduced portion sizes, and the reduced number of food servings being ingested.



Individual dietary supplements

Following is a discussion of individual dietary supplements that may have benefit in the treatment and prevention of dementia.

Ginkgo biloba extract

The research on *Ginkgo biloba* extract in treating dementias and other cognitive functions is vast. As a matter of fact, there are over 120 published clinical studies on Ginkgo (Sierpina, Wollschlaeger & Blumenthal 2003). Consequently, with the exception of a discussion on one clinical trial, it was necessary to limit my presentation of the data to reviews and meta-analyses on the topic.

Eight randomized, double-blind, placebo-controlled studies on Ginkgo extract were systematically reviewed by Kleijnen and Knipschild (1992). The reviewers concluded that that ginkgo had modest effects on improving the symptoms of dementia and cerebral insufficiency. Furthermore, they indicated that the improvement was equivalent to therapy with ergoloid mesylates (Hydergine).

A meta-analysis by Oken, Storzbach and Kaye (1998) included four studies (with a total of 212 subjects in the placebo and Ginkgo groups) that met inclusion criteria for adequate clinical design for examining Ginkgo's effects on objective measures of cognitive function in patients with Alzheimer's disease. The results were that a significant overall effect in the Gingko groups was demonstrated that was comparable with the benefits of donepezil (Aricept).

Wettstein (2000) reviewed studies on Ginkgo that lasted at least six months in duration. He concluded that Ginkgo extract was equally effective in mild to moderate Alzheimer's dementia in comparison to second-generation cholinesterase inhibitors.

Other research reviews on the use of Ginkgo in treating dementia have shown similar beneficial results to those previously discussed (Kidd 1999; Sierpina, Wollschlaeger & Blumenthal 2003).

In what may well be the largest, longest controlled trial of Ginkgo extract to date, LeBars et al. (1997) treated 309 patients with mild to moderately severe forms of dementia of the Alzheimer type (DAT) or multi-infarct dementia (MID), using 120 mg/day or placebo. The evaluation of patients took place periodically, up through 52 weeks of therapy. The results indicated that Ginkgo extract was capable of stabilizing cognitive performance and social functioning in patients with dementia. These changes were objectively quantifiable and noticeable by caregivers, despite the fact that they were classified as modest.

It should be noted that Kidd (2000) criticized the LeBars study due to the fact that 'only 29 percent of their patients benefited from 120 mg per day of GbE [*Ginkgo biloba* extract], to an extent comparable to a six-month delay in disease progression.' Nonetheless, in considering a review of Ginkgo research, Kidd (2000) also acknowledged that Ginkgo's 'cognition-enhancing effects are real, if modest.'

With regard to Ginkgo's safety, Kleijnen and Knipschild's literature review (1992) of human clinical research on the use of Ginkgo extract for cerebral insufficiency and intermittent claudication concluded that Ginkgo's risk for side effects was low. Another safety review was conducted by Chavez and Chavez (1998), and included trials using Ginkgo for a number of other diseases in addition to dementia and peripheral vascular insufficiency. After reviewing over 70 clinical trials, they concluded that adverse effects occurred in less than 1% of patients, and were generally mild in severity. The most frequent adverse effects reported included gastrointestinal disturbances, headache and dermal hypersensitivity. Other research has also documented Ginkgo's safety (Ernst & Pittler 1999; Sierpina, Wollschlaeger & Blumenthal 2003).

Although concerns about drug interactions with Ginkgo and MAO-inhibitors, diuretics or anticonvulsants have been expressed or speculated, these have not proven to have any

demonstrable basis in clinical practice (Blumenthal 2003:185-200). One legitimate drug interaction is an increase risk of bleeding when used in combination with antiplatelet medications such as warfarin (Sierpina, Wollschlaeger & Blumenthal 2003).

A review of the previous research seems to indicate a favorable benefit-to-risk profile of Ginkgo extract therapy in the treatment of dementia. For this purpose, Ginkgo is used as a standardized preparation containing 24% ginkgo flavonoid glycosides and 6% terpene lactones, in a typical range of 120 to 240 mg daily, taken in two to three doses (Sierpina, Wollschlaeger & Blumenthal 2003).

Phosphatidylserine

The phospholipid phosphatidylserine (PS) is active at cell membranes (including synaptic membrane zones) and a major building block for nerve cells (Kidd 1999). A significant amount of published clinical research has demonstrated that PS supplementation supports various cognitive parameters (Kidd 1999). This includes research with dementia patients.

In one study, Engel et al. (1992) treated 33 patients with early dementia of the Alzheimer type with either 300 mg/d of PS or a placebo in a double-blind cross-over design. Treatment lasted eight weeks for each study phase, and there was a washout period in between. The results were that significantly more patients improved with PS than placebo during the phase one of treatment (based upon clinical global improvement ratings); and the improvement lasted through the washout phase and into the next treatment phase. Also, although EEG mapping initially indicated that patients showed higher power values in frequency bands compared to a younger, healthy control group, supplementation with PS successfully reduced the higher power values shifting EEG power more towards the normal level.

A similar double-blind, randomized, controlled study (using the same dosage of PS) was conducted by Delwaide et al. (1986) in 42 hospitalized patients with dementia. Evaluation was based upon the Crichton Scale and the Peri scale (originally designed in the hospitals geriatric unit). A trend toward improvement was seen with the PS patients, and a significant treatment effect was noted on the Peri scale. Three weeks later there was still a statistically significant difference in the Peri Scale, 'indicating that modifications are drug-related.'

In a double-blind study with PS in Parkinsonian patients with dementia of the Alzheimer's type (DAT), Funfgeld et al. (1989) demonstrated that treatment with PS was able to influence cerebral changes contributing to the symptoms of DAT. Specifically, PS promoted the slowing of EEG in Parkinsonian patients with DAT. The researchers also indicated that Theta anteriorisation can be reduced or even abolished, and replaced by Alpha waves. A later study by Funfgeld (1996) demonstrated similar beneficial results in DAT patients treated with 500-700 mg of PS.

In a preliminary trial (Rabboni et al. 1990) of 30 elderly patients with either multi-infarctual dementia (MID), senile dementia of Alzheimer type (DAT) or minor depression, 400 mg/day of PS was given orally for 60 days. Treatment with PS resulted in a significant decrease in the basal scores of the Gottfries-Brane-Steene subscales and Hamilton Depression Scale. Other biochemical parameters also improved. The authors concluded 'Collectively the results indicate that phosphatidylserine exerts an effective improvement in most of these patients with amelioration persisting after drug withdrawal.'

Other research with PS supplementation has also shown improvements in cognitive function in both patients with mild cognitive impairment (Sinforiani et al 1987) and mild dementia (Puca, Savarese & Minervini 1987).

In laboratory tests on serum samples of patients treated with PS, significant reductions in uric acid and SGPT levels were noted (which may be considered beneficial); while all other serum parameters were unaffected (Cenacchi, Baggio & Palin 1987). In addition, PS has a favorable benefit-to-risk profile since, according to Kidd (1999), 'its benefits are often remarkable, adverse effects from its use are virtually never seen, and its compatibility with most common drugs is established.' Most of the research on PS in the treatment of dementias and cognitive dysfunctions indicated an effective daily dosage range of 300-400 mg ('Phosphadidylserine' 1999).

Huperzine A

Huperzine A is a natural substance derived from an extract of *Huperzia serrata*, a Chinese moss. Most of the research conducted on Huperzine A demonstrates that it is a promising new treatment for Alzheimer's disease. The reason for this has to do with acetylcholine.

Acetylcholine is a neurotransmitter (i.e., transmits messages from one nerve cell to another) which is well understood in its role in the central nervous system, relating to memory and cognitive function. There is, however, an enzyme called acetylcholinesterase (AChE) which prevents acetylcholine from performing its cognitive functions. When AChE is released in the body, it inactivates acetylcholine within 1/500 of a second (Tortora & Anagnostakos 1981). Although this is a normal activity, AChE production can sometimes get out of hand. When this happens, it can adversely affect cognitive functions. This is where Huperzine A comes in.

Huperzine A is a selective AChE inhibitor (Zhang et al. 1991; Ashani et al. 1994; Raves et al. 1997). As such, it is able to allow for higher levels of acetycholine. The cognitive benefits of this were demonstrated in a double-blind study where a statistically significant improvement was achieved in patients with multi-infarct, senile dementia, and presenile simple memory disorder. The effective dose used in this study was 30 to 50 mcg of Huperzine A, twice daily (Zhang et al. 1991). Similar research has shown memory, cognition, and behavior improvements in Alzheimer's patients (Xu et al. 1995). Other research has shown that Huperzine A has an ability to reduce neuronal cell death (caused by exposure to a toxin) (Ved et al. 1997), and has been used in patients with myasthenia gravis (a debilitating disease associated with wasting of muscles) (Zhang et al. 1991).

Vinpocetine

Vinpocetine is a natural substance derived from Periwinkle seeds. Research in Europe has demonstrated that Vinpocetine can help improve cognitive function and short-term memory in both animals and humans (Ishihara et al. 1989; Pepeu & Spignoli 1989; Bhatti & Hindmarch 1987; Subhan & Hindmarch 1985; DeNoble1987). Other research indicates that Vinpocetine is effective for patients with cerebrovascular disease (Miyazaki 1995; Hayakawa1992; Szobor & Klein 1992). One of Vinpocetine's identified mechanisms of action is improvement in brain circulation and oxygen utilization (Kiss & Karpati 1996) (although Ginkgo biloba also improves brain circulation, it does not have Vinpocetine's other functions). An improvement in brain circulation means that all of the nutrients that the brain needs to concentrate and function properly, are able to be effectively delivered. Improved oxygen utilization means that the brain should be more effective at producing ATP (the energy "currency" of the body). In fact, research has shown that vinpocetine effectively elevated cerebral concentrations of ATP (Kakihana et al. 1982), as well as ATP concentrations in red blood cells (Tohgi 1990). More ATP means more brain energy. More brain energy means an ability to concentrate.

In addition to its circulation and oxygen enhancing properties, another mechanism of

Vinpocetine's action is that it seems to work as part of the cholinergic pathway (Pepeu & Spignoli 1989). This is the pathway that involves the production of the memory neurotransmitter, acetylcholine. Specifically, Vinpocetine increases the firing rate of certain nerve cells (Gaal & Molnar 1990).

Finally, Vinpocetine is a remarkable safe substance. Miskolczi et al (1990) concluded that there is no accumulation or autoinduction of Vinpocetine at doses up to 30 mg daily. Other research has also shown that Vinpocetine has no serious side effects (Balestreri 1987). Actually, Vinpocetine is not only safe, but is actually an effective antioxidant against free radicals (Olah et al. 1990). Human research on Vinpocetine has utilized around 10 to 15 mg daily.

Alpha-GPC

Alpha-glycerylphosphorylcholine (Alpha-GPC) is an acetylcholine precursor derived from soy. Research has demonstrated that Alpha-GPC increases acetylcholine release (Ceda et al. 1992). Not surprisingly, it is used for the treatment of cognitive disorders of aging. Alpha GPC was found to produce definite symptomatic improvement and showed good tolerability in the treatment of patients with mild to moderate vascular dementia (Di Perri et al. 1991). Similarly, the administration of Alpha GPC resulted significant improvements among patients with probable Alzheimer's dementia (Parnetti et al. 1993). In patients with acute cerebrovascular disease, Alpha GPC helped promote functional recovery of patients with cerebral stroke (Parnetti et al. 2001). Likewise, in a study involving 2044 patients suffering from recent stroke or transient ischemic attacks, Alpha GPC was administered on a daily basis after the attack. As a result, 71% of the patients experienced "no cognitive decline" or "forgetfulness" (Barbagallo Sangiorgi et al. 1994).

Acetyl-L-carnitine

Acetyl-L-carnitine is an ester derivative of the amino acid l-carnitine, with many important biochemical properties. Several clinical trials have found that acetyl-L-carnitine supplementation delays the progression of Alzheimer's disease (Pettegrew et al. 1995), improves memory (Salvioli & Neri 1994; Rai et al. 1990; Sano et al. 1992) and enhances overall performance in some people with Alzheimer's disease (Cucinotta et al. 1988; Bonavita et al. 1986). However, in one double-blind trial, people who received acetyl-L-carnitine (1 gram three times per day) deteriorated at the same rate as those given a placebo (Thal et al. 1996). Overall, however, most short-term studies have shown clinical benefits, and most long-term studies (one year) have shown a reduction in the rate of deterioration (Calvani et al. 1992). A typical supplemental amount is 1 gram taken three times per day.

Vitamin B-12

Certain studies have indicated that Alzheimer's patients often have significantly lower serum vitamin B-12 than control subjects. Furthermore, some of these studies suggest the possibility of a specific relationship between B-12 levels and severity of cognitive impairment in patients with AD. In a related study, researchers found that individuals using dietary supplements (i.e., multiple vitamin) had significantly higher biochemical values for vitamin B-12, as well as certain other B vitamins, than nonsupplement users (Levitt & Karlinsky 1992; Gottfries 1990; Renvall 1989).

Free radicals and antioxidants

Free radicals are extremely unstable molecules which, in the presence of oxygen, will turn a shiny metal wrench into an ugly rusted wrench very quickly. In humans, free radicals cause irreparable oxidative damage to cells and the protective membrane linings that surround cells. Some common sources of free radicals are smoking, consumption of fats, inhalation of carbon

monoxide and other environmental pollutants, chemical additives in foods such as nitrites and nitrates, overexposure to the sun and other sources of radiation (Kronhuasen 1989).

Evidence implicating the free radical oxidative processes in the pathogenesis of Alzheimer's disease is rapidly accumulating. This includes research which has identified free radical oxidation products in the blood serum of patients with senile dementia of the Alzheimer type. Furthermore, these same patients have a statistically significant decrease in their serum levels of certain antioxidants including glutathione peroxidase, vitamins E, C and A, and the mineral zinc. In another study, nearly 60% of Alzheimer patients had serum vitamin E levels below the accepted normal range. The results of this type of research lends credence to the conclusion of one group of Alzheimer's disease researchers, "The possible modulation of free radical oxidative activity by antioxidant micronutrients and pharmacological agents, provides a rational basis for further preventative and therapeutic clinical investigations" (Evans et al. 1992; Jeandel et al. 1989; Burns & Holland 1986).

In addition, supplemental vitamin E may slow the progression of Alzheimer's disease. A double-blind trial found that 2,000 IU of vitamin E per day for two years extended the length of time people with moderate Alzheimer's disease were able to continue caring for themselves (e.g., bathing, dressing, and other necessary daily functions), compared with people taking a placebo (Sano et al. 1997).

Also, in a preliminary trial people with early Parkinson's disease given 750 mg of vitamin C and 800 IU of vitamin E four times each day (totaling 3,000 mg of vitamin C and 3,200 IU of vitamin E per day) were able to delay the need for drug therapy (i.e., L-dopa or selegiline) by an average of about two and a half years, compared with those not taking the vitamins Fahn 1992).

Green tea also provides a rich source of antioxidants that may have benefit in the prevention of cognitive dysfunction. In one study, a higher consumption of green tea was associated with a lower prevalence of cognitive impairment in humans (Kuriyama et al. 2006).

Phosphatidyl choline

In one study, it was observed that among Alzheimer's patients, the theoretical choline uptake into choline-depleted red blood cells was strongly correlated with the severity of the dementia. In other words, the less choline, the more severe the dementia. Subsequent or concurrent studies had conflicting results regarding the benefit of administering phosphatidyl choline supplements to Alzheimer's patients. Some research demonstrated moderate improvements in orientation, learning and memory, while other research showed no improvement. In one of the "no improvement" studies, however, 12 out of 13 patients showed no evidence of deterioration over the study period; thus suggesting that phosphatidyl choline may delay the rate of progression of the disease (Konof 1985; Dysken 1987; Little et al 1985; Weintraub et al. 1983; Fisman et al. 1981; Brinkman et al. 1982).

Coenzyme Q10

Co-enzyme Q_{10} is a vitamin-like substance involved in cellular energy metabolism. It is also an antioxidant, like vitamin C, that is beneficial in the prevention and treatment of various cardiovascular disorders, including angina, congestive heart failure, and hypertension (Bruno 2001). In a double-blind trial, administration of 1,200 mg of coenzyme Q10 per day for 16 months to people with early Parkinson's disease significantly slowed the progression of the disease, compared with a placebo (Shults et al. 2002). Smaller amounts of CoQ10 were slightly more effective than placebo, but the difference was not statistically significant.

Natural protocols for different types of dementia

The following natural protocols are in no way intended as a replacement of the care provided by licensed healthcare professionals. As a matter of fact, I encourage all nutrition professionals to work cooperatively with your client's physician, especially in the case of dementia.

These protocols are only general suggestions. Clearly, an individual approach to each client will yield the best results.

Please note that for general nutritional purposes, as well as to provide some specific antioxidants and other nutrients with benefit in the treatment or prevention of dementias, each protocol will begin with a basic foundation program (BFP). A BFP consists of optimal doses of all of the basic vitamins and minerals. Many individuals wrongly assume that a single multiple vitamin product will provide this. However, unless the multiple vitamin were the size of a golf ball, its size would be inadequate to provide optimal doses of each vitamin and mineral. A more realistic approach is to obtain optimal doses from four dietary supplements: A multiple vitamin product (with a 50-75 mg B-complex), a vitamin C product (500-1000 mg), a vitamin E product (400 IU), and a multiple mineral product (with 500-600 mg calcium).

Alzheimer's disease	
Primary Recommendations	*Dosage*
BFP	4 tablets taken with breakfast or lunch
Ginkgo biloba (24% flavonoid glycosides and 6% terpene lactones)	120 to 240 mg daily, taken in two to three doses
Acetyl-L-Carnitine	3000 mg daily, taken in three doses
Vitamin E (d-alpha)	2,000 IU daily
Huperzine A	60 to 100 mcg daily, taken in two doses
Phosphatidylserine	300 to 700 mg daily, taken in two to three doses
Secondary Recommendations	*Dosage*
Vinpocetine	10 to 15 mg daily
Phosphatidyl choline	900 mg daily
Green tea	3 cups daily
Vitamin B12 (sublingual)	If deficient, 1,000 mcg twice weekly

Vascular dementia	
Primary Recommendations	*Dosage*
BFP	4 tablets taken with breakfast or lunch
Ginkgo biloba (24% flavonoid glycosides and 6% terpene lactones)	120 to 240 mg daily, taken in two to three doses
Vitamin E (d-alpha)	800 IU daily
Huperzine A	60 to 100 mcg daily, taken in two doses
Alpha-GPC	1,200 mg daily
Vinpocetine	10 to 15 mg daily
Cardiovascular support supplements (Coenzyme Q10, Policosanol, etc.)	Varying
Secondary Recommendations	*Dosage*
Phosphatidylserine	300 to 700 mg daily, taken in two to three doses
Green tea	3 cups daily

Parkinson's disease	
Primary Recommendations	*Dosage*
BFP	4 tablets taken with breakfast or lunch
Coenzyme Q10	1,200 mg daily
Vitamin E (d-alpha)	3,200 IU daily, taken in four divided doses (Note: this high dose should only be used when working with a physician monitoring serum vitamin E levels)
Vitamin C	3,000 mg daily, taken in three to four divided doses
Phosphatidylserine	300 daily, taken in two to three doses
Secondary Recommendations	*Dosage*
Ginkgo biloba (24% flavonoid glycosides and 6% terpene lactones)	120 to 240 mg daily, taken in two to three doses
Green tea	3 cups daily

CONCLUSION

The treatment of the dementias requires a multifaceted approach. Ideally, this includes a family support structure, a healthcare professional support structure, proper nutrition for the elderly, and the use of select dietary supplements.

REFERENCES

Alzheimer's Society, Accessed September 8, 2006 from http://www.alzheimers.org.uk/VascularDementia/seminars_Cardiff.htm.

Alzheimer's Association, Accessed May 5, 2004 from http://www.alz.org/overview.asp.

Alzheimer's Association, Accessed September 8, 2006 from http://www.alz.org/AboutAD/WhatIsAD.asp.

Ashani, Y., Grunwald, J., Kronman, C., Velan, B., Shafferman, A. 1994, 'Role of tyrosine 337 in the binding of huperzine A to the active site of human acetylcholinesterase', *Mol Pharmacol*, vol. 45, no. 3, pp. 555-560.

Barbagallo Sangiorgi, G., Barbagallo, M., Giordano, M., Meli, M., Panzarasa, R. 1994, 'alpha-Glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial', *Ann N Y Acad Sci*, vol. 717, pp. 253-69.

Balestreri, R., Fontana, L., Astengo, F. 1987, 'A double-blind placebo controlled evaluation of the safety and efficacy of vinpocetine in the treatment of patients with chronic vascular senile cerebral dysfunction', *J Am Geriatr Soc*, vol. 35, no. 5, pp. 425-30.

Beach, D.L., 1997.'Family caregiving: the positive impact on adolescent relationships', *Gerontologist*, vol. 37, no. 2, 233-8.

Bhatti, J., Hindmarch, I. 1987, 'Vinpocetine effects on cognitive impairments produced by flunitrazepam', *Int Clin Psychopharmacol*, vol. 2, no. 4, pp. 325-31.

Blumenthal, M. (ed) 2003, *The ABC Clinical Guide to Herbs*, American Botanical Council, Austin, Texas.

Bonavita, E. 1986, 'Study of the efficacy and tolerability of L-acetylcarnitine therapy in the senile brain', *Int J Clin Pharmacol Ther Toxicol*, vol. 24, pp. 511–6.

Brinkman, S.D., et al. 1982. 'A dose-ranging study of lecithin in the treatment of primary degenerative dementia (Alzheimer disease)', *Brief Reports*, vol. 2, pp. 281-5.

British Nutrition Foundation 1996. 'Nutrition in older people. Briefing Paper', British Nutrition Foundation, London, pp. 1-27.

Bruno, G. 2001, *Ailments & Natural Remedies*, New York: Fifty-Ninth Street Bridge Publishing Corp.

Burns, A., Holland, T. 1986, 'Vitamin E deficiency. Letter to the editor', *Lancet*, April 5, pp. 805-6.

Calvani, M., Carta, A., Caruso, G., et al. 1992, 'Action of acetyl-L-carnitine in neurodegeneration and Alzheimer's disease', *Ann NY Acad Sci*, vol. 663, pp. 483–6.

Ceda, G.P., Ceresini, G., Denti, L., Marzani, G., Piovani, E., Banchini, A., Tarditi, E., Valenti, G. 1992, 'alpha-Glycerylphosphorylcholine administration increases the GH responses to GHRH of young and elderly subjects', *Horm Metab Res*, vol. 24, no. 3, pp.119-21

Cenacchi, T., Baggio, C. & Palin, E. 1987, 'Human tolerability of oral phosphatidylserine assessed through laboratory examinations. *Clin Trials J*, vol. 24, no. 1, pp. 125-130.

Chavez, M.L. and Chavez, P.I. 1998, 'Ginkgo (Part 2): Clinical efficacy, dosage, and adverse effects', *Hosp Pharm*, vol. 33, no. 9, pp. 1076–1095.
Chernoff R. 2003. 'Normal aging, nutritional assessment, and clinical practice', *Nutrition in Clinical Practice*, vol. 18, pp. 12-20.
Cucinotta, D., et al. 1988, 'Multicenter clinical placebo-controlled study with acetyl-L-carnitine (LAC) in the treatment of mildly demented elderly patients', *Drug Development Res*, vol. 14, pp. 213–6.
Delwaide, P.J., Gyselynck-Mambourg, A.M., Hurlet, A. & Ylieff, M. 1986, 'Double-blind randomized controlled study of phosphatidylserine in senile demented patients', *Acta Neurologica Scandinavica*, vol. 73, no. 2, pp. 136-40.
DeNoble, V. 1987, 'Vinpocetine enhances retrieval of a step-through passive avoidance response in rats', *Pharmacol Biochem Behav*, vol. 26, no. 1, pp. 183-6.
Di Perri, R., Coppola, G., Ambrosio, L.A., Grasso, A., Puca, F.M., Rizzo, M. 1991, 'A multicentre trial to evaluate the efficacy and tolerability of alpha-glycerylphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia', *J Int Med Res*, vol. 19, no. 4, pp. 330-41.
Dysken, M. 1987, 'A review of recent clinical trials in the treatment of Alzheimer's dementia', *Psychiatric Annals*, vol. 17, no. 3, pp. 178.
Engel, R.R., Satzger, W., Gunther, W., Kathmann N; Bove, D., Gerke, S., Munch, U. & Hippius, H. 1992, 'Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type' *European Neuropsychopharmacology*, vol. 2, no. 2, pp. 149-55.
Ernst, E. & Pittler, M.H. 1999, 'Ginkgo biloba for dementia. A systematic review of double-blind, placebo-controlled trials', *Clin Drug Invest*, vol. 17, pp. 301-8.
Evans, P.H., et al. 1992, 'Oxidative damage in Alzheimer's dementia, and the potential etiopathogenic role of aluminosilicates, microglia and micronutrient interactions', *EXS*, vol. 62, pp. 178-89.
Fahn, S. 1992, 'A pilot trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's disease', *Ann Neurol*, vol. 32, pp. S128–32.
Family Caregiving Alliance, Accessed May 5, 2004. http://www.caregiver.org/caregiver/jsp/home.jsp
Fisman, M., et al. 1981, 'Double blind study of lecithin in patients with Alzheimer's disease', *Can J Psychiat*, vol. 26, pp. 426-8.
Fuh, J. L., Wang, S.J., Liu, H.C., Liu, C.Y., Wang, H.C. 1999, 'Predictors of depression among Chinese family caregivers of Alzheimer Patients', *Alzheimer disease and associated disorders*, vol. 13, no. 3, pp. 171-5.
Funfgeld, E.W. 1996, 'Statistical reliability of the cerebral action of Nootropics with the Brain Mapping and the computerized 20-frequency band analysis of the EEG in case of presenile/senile. Alzheimer disease (AD/SDAT). The second report: Findings after phosphatidylserine", *Geriatr Forsch*, vol. 6, no. 1, pp. 19-33.
Funfgeld, E.W., Baggen, M., Nedwidek, P., Richstein, B. & Mistlberger, G. 1989, 'Double-blind study with phosphatidylserine (PS) in parkinsonian patients with senile dementia of Alzheimer's type (SDAT)', *Progress in Clinical and Biological Research*, vol. 317, pp. 1235-46.
Gaal, L., Molnar, P. 1990, 'Effect of vinpocetine on noradrenergic neurons in rat locus coeruleus', *Eur J Pharmacol*, vol. 187, no. 3, pp. 537-9.
Gerrior, S.A. 1999. 'Dietary Changes in Older Americans From 1977 to 1996: Implications for Dietary Quality', *Family Economics and Nutrition Review*, vol. 12, no. 2, pp. 3-14.
Gottfries, C.G. 1990, 'Pharmacological treatment strategies in Alzheimer type dementia', *Eur Neuropsychopharmacol*, vol. 1, no. 1, pp. 1-5.
Hayakawa, M. 1992, 'Effect of vinpocetine on red blood cell deformability in vivo measured by a new centrifugation method', *Arzneimittelforschung*, vol. 42, no., pp. 281-3.
Ishihara, K., Katsuki, H., Sugimura, M., Satoh, M. 1989. 'Idebenone and vinpocetine augment long-term potentiation in hippocampal slices in the guinea pig', *Neuropharmacology*, vol. 28, no. 6, pp. 569-73.
Jacques, A. & Jackson, G.A. 2000, *Understanding Dementia*, 2nd ed., Churchill Livingstone, Edinburgh.
Jeandel, C., et al. 1989, 'Lipid peroxidation and free radical scavengers in Alzheimer's disease', *Gerontology*, vol. 35, no. 5-6, pp. 275-82.
Johnson, K.A., Bernard, M.A. & Funderburg, K. 2002. 'Vitamin nutrition in older adults', *Clinics in Geriatric Medicine*, vol. 18, pp. 773–799.
Kakihana, M., Suno, M., Shibota, M., Hamajo, K., Nagaoka, A. 1982, 'Protective effect of vinpocetine on experimental brain ischemia', *Nippon Yakurigaku Zasshi*, vol. 80, no. 3, pp. 225-9.
Kidd, P.M. 1999, 'A review of nutrients and botanicals in the integrative management of cognitive dysfunction', *Alternative Medicine Review*, vol. 4, no. 3, pp. 144-61.
Kiss, B., Karpati, E. 1996, 'Mechanism of action of vinpocetine', *Acta Pharm Hung*, vol. 66, no. 5, pp. 213-24.
Kleijnen, J. & Knipschild, P. 1992, 'Ginkgo biloba for cerebral insufficiency', *Br J Clin Pharmacol*, vol. 34, pp. 352-8.
Kleijnen, J. & Knipschild, P. 1992, 'Ginkgo biloba', *Lancet*, vol. 340, pp. 1136–1139.
Konof, P. 1985, 'Red blood cell choline', *Biol Psychiat*, vol. 20, pp.375-83.

Kronhuasen, K. 1989, *Formula for life.* New York: William Morrow & Co.
Kuriyama, S., Hozawa. A., Ohmori, K., Shimazu, T., Matsui, T., Ebihara, S., Awata, S., Nagatomi, R., Arai, H., Tsuji, I. 2006, 'Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project', *Am J Clin Nutr*, vol. 83, no. 2, pp. 355-61.
LeBars, P.L., Katz, M.M., Berman, N., Itil, T.M., Freedman, A.M. & Schatzberg, A. 1997, 'A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia', *JAMA*, vol. 278, pp. 1327–1332.
Levitt, A.J., Karlinsky, H. 1992, 'Folate, vitamin B-12 and cognitive impairment in patients with Alzheimer's disease', *Acta Psychiatr Scand*, vol. 86, no. 4, pp. 301-5.
Little, A., et al. 1985, 'A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease', *J Neurol Neurosurg & Psychiat*, vol. 48, pp. 736-42.
McClain, C.J., McClain, M., Barve, S. & Boosalis, M.G. 2002. 'Trace metals and the elderly', *Clinics in Geriatric Medicine*, vol. 18, pp. 801-818.
McGee, S., Albernethy, W. III, & Simel, D.L. 1999. 'Is this patient hypovolemic?' *Journal of the American Medical Association*, vol. 281, pp. 1022-1029.
McGee, M. & Jensen, G.L. 2000. 'Nutrition in the Elderly,' *Journal of Clinical Gastroenterology*, vol. 30, no. 4. pp. 372-380.
Meyyazhagan, S. & Palmer, R.M. 2002. 'Nutritional requirements with aging: Prevention of disease', *Clinics in Geriatric Medicine*, vol. 18. pp. 557–576.
Miskolczi, P., Kozma, K., Polgar, M., Vereczkey, L. 1990, 'Pharmacokinetics of vinpocetine and its main metabolite apovincaminic acid before and after the chronic oral administration of vinpocetine to humans', *Eur J Drug Metab Pharmacokinet*, vol. 15, no. 1, pp. 1-5.
Miyazaki, M., 1995, 'The effect of a cerebral vasodilator, vinpocetine, on cerebral vascular resistance evaluated by the Doppler ultrasonic technique in patients with cerebrovascular diseases', *Angiology*, vol. 46, no. 1, pp. 53-8.
National Family Caregiver Support Program, Accessed May 5, 2004. http://www.aoa.gov/prof/aoaprog/caregiver/overview/overview_caregiver.asp.
National Family Caregivers Association, Accessed May 5, 2004. http://www.nfcacares.org/.
National Parkinson Foundation, Accessed September 8, 2006 from http://www.parkinson.org/site/pp.asp?c=9dJFJLPwB&b=71125.
National Respite Locator Service, Accessed May 5, 2004 from http://www.respitelocator.org/index.htm.
Oken, B.S., Storzbach D.M. & Kaye J.A. 1998, 'The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease', *Arch Neurol*, vol. 55, pp. 1409-15.
Olah, V.A., Balla, G., Balla, J., Szabolcs, A., Karmazsin, L. 1990, 'An in vitro study of the hydroxyl scavenger effect of Cavinton', *Acta Paediatr Hung*, vol. 30, no. 2, pp. 309-16.
Parnetti, L., Abate, G., Bartorelli, L., Cucinotta, D., Cuzzupoli, M., Maggioni, M., Villardita, C., Senin, U. 1993, 'Multicentre study of l-alpha-glyceryl-phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type', *Drugs Aging*, vol. 3, no. 2, pp. 159-64.
Parnetti, L., Amenta, F., Gallai, V. 2001, 'Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data', *Mech Ageing Dev*, vol. 122, no. 16, pp. 2041-55.
Pepeu, G., Spignoli, G. 1989, 'Nootropic drugs and brain cholinergic mechanisms', *Prog Neuropsychopharmacol Biol Psychiatry*, 13 Suppl, pp. S77-88.
Pettegrew, J.W., Klunk, W.E., Panchalingam, K., et al. 1995, 'Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease', *Neurobiol Aging*, vol. 16, pp. 1–4.
'Phosphadidylserine' 1999, *Alternative Medicine Review*, vol. 4, no. 2, pp. 115-17.
Puca, F.M., Savarese, M.A. & Minervini, M.G. 1987, 'Exploratory trial of phosphatidylserine efficacy in mildly demented patients. *Clin Trials J*, vol. 24, no. 1, pp. 94-98.
Rabboni, M., Maggioni, F.S., Giannelli, A. & Beinat, L. 1990, 'Neuroendocrine and behavioural effects of phosphatidylserine in elderly patients with abiotrophic or vascular dementia or mild depression. A preliminary trial', *Clin Trials J*, vol. 27, no. 3, pp. 230-240.
Rai, G., Wright, G., Scott, L., et al. 1990, 'Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia', *Curr Med Res Opin*, vol. 11, pp. 638–47.
Raves, M.L., Harel, M., Pang, Y.P., Silman, I., Kozikowski, A.P., Sussman, J.L. 1997, 'Structure of acetylcholinesterase complexed with the nootropic alkaloid, (-)- huperzine A', *Nat Struct Biol*, vol. 4, no. 1, pp. 57-63.
Renvall, M.J., et al. 1989, 'Nutritional status of free-living Alzheimer's patients. *Am J Med Sci*, vol. 298, no. 1, pp. 20-7.
Russell, R.M., Rasmussen, H. & Lichtenstein, A.H. 1999. 'Modified Food Guide Pyramid for People over Seventy Years of Age', *Journal of Nutrition*, vol. 129, pp. 751-753.
Salvioli, G., Neri, M. 1994, 'L-acetylcarnitine treatment of mental decline in the elderly', *Drugs Exp Clin Res*, vol. 20, pp. 169–76.

Sano, M., Bell, K., Cote, L., et al. 1992, 'Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease', *Arch Neurol*, vol. 49, pp. 1137–41.
Sano, M., Ernesto, C., Thomas, R.G., et al. 1997, 'A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease', *N Engl J Med*, vol. 336, pp. 1216–22.
Shults, C.W., Oakes, D., Kieburtz, K., et al. 2002, 'Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline', *Arch Neurol*, vol. 59, pp. 1541–50.
Sierpina, V.S., Wollschlaeger, B. & Blumenthal, M. 2003, 'Ginkgo biloba', *American Family Physician*, vol. 68, no. 5, pp. 923-6.
Sinforiani, E., Agostinis, C., Merlo, P., Gualteri, S., Mauri, M. & Mancuso, A. 1987, 'Cognitive decline in ageing brain. Therapeutic approach with phosphatidylserine', *Clin Trials J*, vol. 24, no. 1, pp. 115-124.
Spence, A.P. 1999, *Biology of Human Aging*, 2nd ed., Prentice Hall, Upper Saddle River, New Jersey.
Stechmiller, J.K. 2003. 'Early Nutritional Screening of Older Adults: Review of Nutritional Support', *Journal of Infusion Nursing*, vol. 26, no. 3, pp. 170-177.
Subhan, Z., Hindmarch, I. 1985, 'Psychopharmacological effects of vinpocetine in normal healthy volunteers', *Eur J Clin Pharmacol*, vol. 28, no. 5, pp, 567-71.
Szobor, A., Klein, M. 1992, 'Examinations of the relative fluidity in cerebrovascular disease patients', *Ther Hung*, vol. 40, no. 1, pp. 8-11.
Thal, L.J., Carta, A., Clarke, W.R., et al. 1996, 'A 1-year multi-center placebo-controlled study of aceyl-L-carnitine in patients with Alzheimer's disease', *Neurology*, vol. 47, pp. 705–11.
Tohgi, H., Sasaki, K., Chiba, K., Nozaki, Y. 1990, 'Effect of vinpocetine on oxygen release of hemoglobin and erythrocyte organic polyphosphate concentrations in patients with vascular dementia of the Binswanger type', *Arzneimittelforschung*, vol. 40, no. 6, pp. 640-3.
Tortora, G., Anagnostakos N., 1981. *Principles of Anatomy and Physiology, Third Edition,* New York: Harper & Row.
Ved, H.S., Koenig, M.L., Dave, J.R., Doctor, B.P. 1997, 'Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate', *Neuroreport*, vol. 8, no. 4, pp. 963-8.
Weintraub, S., et al. 1983, 'Lecithin in the treatment of Alzheimer's disease', *Arch Neurol*, vol. 40, pp. 527.
Wettstein, A. 2000, 'Cholinesterase inhibitors and Ginkgo extracts — are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration', *Phytomedicine*, vol. 6, pp. 393-401.
Whitney, E.N., Cataldo, C.B. & Rolfes, S.R. 1998, *Understanding Normal and Clinical Nutrition*, 5th ed., West/Wadsworth, Belmont, California.
Woudstra, T., Thomson, A.B.R. 2002. 'Nutrient absorption and intestinal adaptation with ageing', *Bailliere's Best Practice and Research in Clinical Gastroenterology*, vol. 16, no. 1, pp. 1-15.
Wijeratne, C., 1997. 'Review: pathways to morbidity in carers of dementia sufferers', *International psychogeriatrics*, vol. 9, no. 1, pp. 69-79.
Xu, S.S., Gao, Z.X., Weng, Z., et al. 1995, 'Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease', *Chung Kuo Yao Li Hsueh Pao*, vol. 16, pp. 391–5.
Zhang, R.W., Tang, X.C., Han Y.Y., et al. 1991, 'Drug evaluation of huperzine A in the treatment of senile memory disorders.' *Chung Kuo Yao Li Hsueh Pao*, vol. 12, no. 3, pp. 250-2.