INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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As promised, here is the final installment of Dr. Ware's comprehensive review of Alzheimer's disease and related dementias. In this part Dr. Ware discusses what you can do to prevent AD or slow its progression. High on the list is supplementing with vitamins E and C. Although vitamin E has been proven most effective it should always be taken with vitamin C as vitamin C helps regenerate it. Vitamin E is also important in preventing and slowing down mild cognitive impairment (MCI) and the herb, ginkgo biloba is another excellent supplement for MCI, especially for short-term memory preservation.

Also in this issue some fascinating research into the optimum timing of vitamins E and C supplementation, new information on the importance of magnesium for heart health, particularly following bypass surgery, and a warning about the growing problem of fructose intolerance. Last, but not least, some new research from the Netherlands that questions the wisdom of treating older people with cholesterol-lowering medications.

Enjoy!

Yours in health,
Hans Larsen, Editor

October Highlights

LETTERS TO THE EDITOR

I've been reading your excellent information on folic acid and have an important, unanswered question. My blood test results show a huge overabundance of folic acid and B-12 in my blood. I take 1 multi-vitamin about once a week, because I forget to take them more often, and I find it hard to believe that my levels are over 1000 higher than they're supposed to be! Do you have any information, articles, or feedback on what this can mean?

KB, USA

Editor: *I have had a few people report abnormally high B12 and folic acid levels, but unfortunately, I have been unable to find out what the cause might be. Are you sure of the units of your measurement? The normal blood serum values for B12 and folate are in the range of:*

Folate: 1.9 - 14.0 ng/mL
Vitamin B12: 200 - 850 pg/mL

Ng stands for nanogram which is 1 billionth (10-9) of a gram. Pg stands for picogram and is 1 trillionth (10-12) of a gram.

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I understand that ginger and turmeric may help cure cancer. How much should one use?

PP, USA

Editor: *The idea that ginger and turmeric can help cure cancer is still very much in the research stage. So far, the only finding is that extracts of turmeric and ginger stop the growth of human cancer cells. There are, as far as I know, no recommendations as*

yet in regards to how much to take. Including turmeric (curcumin) and ginger in your diet would probably be a good idea and is not likely to be harmful unless you are undergoing chemotherapy, in which case, curcumin is not recommended as it may interfere with the treatment.

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Where might I find pharmaceutical grade fish oil?

CR, USA

Editor: *I believe "pharmaceutical grade" fish oil is just another term for molecular distilled fish oil. Most reputable brands are now molecular distilled. I use Coromega brand myself (http://www.coromega.com) and have found it to be an excellent product. You can also find information about pharmaceutical grade fish oil at www.drsears.com. Finally you can find a list of acceptable fish oils at www.consumerlab.com/results/omega3.asp.*

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I am researching the relationship between folic acid supplementation and erythrocytosis (an increase in red blood cell mass). I am experiencing somewhat elevated hematocrit levels (low to mid fifties) and hemoglobin levels (upper 16 to mid 17). Is it possible that 400-800 mcg of folic acid daily could contribute to this problem?

TJB, USA

Editor: *Supplementation with iron and folic acid together will increase both hematocrit and hemoglobin - at least in pregnant women. There is also some evidence that people who are low in folic acid have low hematocrit and hemoglobin. So yes, I would say there could be a connection, particularly if your iron intake is high.*

ABSTRACTS

Timing of antioxidant supplementation is important

ALBUQUERQUE, NEW MEXICO. It is estimated that over 70% of patients with type 2 diabetes eventually die of cardiovascular disease. The development of cardiovascular disease, in turn, involves oxidative stress leading to the release of inflammatory mediators, oxidation of low-density cholesterol lipoprotein (LDL), and the creation of an environment favourable to blood clotting (prothrombotic state). The presence of inflammatory mediators can be determined through measurement of blood levels of CRP (C-reactive protein) and a tendency to increased blood clotting is indicated by an increased level of PAI-1 (plasminogen activator inhibitor-1).

Several studies have shown that high fat meals raise LDL levels, create inflammation, and increase blood clotting tendency in diabetics. Researchers at the New Mexico School of Medicine reasoned that if oxidative stress is the underlying cause of the inflammation and increased blood clotting tendency then antioxidants taken before meals should be beneficial. Their clinical trial involved 11 patients with type 2 diabetes who were exposed to four different test conditions over four 2-day periods. The first day involved consuming a standard dinner at 6 pm and a snack at 10 pm. The next day the participants consumed a standardized breakfast at 8 am and a standardized lunch at 1 pm. At 6 pm the participants were fed a high-fat test dinner equivalent to a McDonald's "Big Mac" meal (70 g fat). The four test periods differed in that in period 1 no antioxidants were given, in period 2 800 IU of natural vitamin E and 1000 mg of vitamin C were taken at the beginning of breakfast, and in period 3 800 IU of natural vitamin E and 1000 mg of vitamin C were taken at the beginning of dinner. Period 4 was a control with no high-fat dinner and no vitamins.

The researchers found that vitamin E levels rose substantially after taking vitamin E at breakfast and stayed high during the day. Vitamin C levels, on the other hand, increased after breakfast, but had decreased by supper time. Both pre-breakfast and pre-supper vitamins C and E supplementation prevented the increase in CRP caused by the high-fat meal with pre-supper vitamins being the most protective. The high-fat evening meal also caused a marked increase in PAI-1 levels; however, this increase was totally avoided if vitamins C and E

were given at breakfast, but remained if the vitamins were only taken at supper time.

The researchers conclude that morning supplementation with vitamin E combined with slow-release vitamin C may be the optimum protocol for preventing high-fat evening meal induced inflammation and blood clotting.

Carroll, Mary F. and Schade, David S. Timing of antioxidant vitamin ingestion alters postprandial proatherogenic serum markers. **Circulation**, *Vol. 108, July 8, 2003, pp. 24-31*

Editor's Comment: Although this study was limited to diabetes patients there is no reason why taking vitamins E and C with breakfast and vitamin C with supper (or use a timed release vitamin C formulation at breakfast) should not be equally protective for healthy individuals against the inflammatory and blood clotting effects of high-fat meals.

Magnesium levels and bypass surgery

DURHAM, NORTH CAROLINA. Coronary artery bypass graft surgery (CABG) is one of the most common operations performed in the United States with over half a million procedures performed in 1995. Unfortunately, the 1-year mortality rate is between 3 and 20% depending on the patient's health status prior to surgery. Researchers at Duke University Medical Center now report that the patient's magnesium status immediately following surgery is a major factor in determining 1-year survival. The study involved 957 patients undergoing primary CABG. All patients had their serum magnesium level measured daily during the 8 days following surgery. A magnesium level below 1.8 mmol/L was considered low. A total of 182 patients (19%) had a low magnesium level while the remaining 787 patients (81%) were categorized as having normal levels.

One year following surgery 75 patients in the group of 957 had died and 22 had suffered a heart attack. The risk of death or a heart attack was 26% lower in the normal magnesium level group. Overall, patients with a magnesium level below 1.8 mmol/L during the first 8 days after surgery were twice as likely to have a heart attack (myocardial infarction) or to die within the first year after CABG as were patients with normal magnesium levels.

The researchers point out that serum magnesium levels are a very poor indicator of total body magnesium levels and that measuring intracellular levels would be more indicative. They found no relationship between magnesium levels and the incidence of atrial arrhythmias after the operation. The researchers speculate that the ability of magnesium to prevent postoperative death may be related to its ability to protect against free radical formation and to counteract the calcium overload inherent in reperfusion. Magnesium supplementation also reduces acute platelet dependent blood clotting and may help prevent ventricular arrhythmias. The researchers recommend that a clinical trial be carried out to investigate the benefits of magnesium treatment prior to CABG surgery.

Booth, John V., et al. Low serum magnesium level predicts major adverse cardiac events after coronary artery bypass graft surgery. **American Heart Journal**, *Vol. 145, June 2003, pp. 1108-13*

Editor's comment: This study supports the idea that magnesium is of prime importance for heart health. Other studies have shown that about a third of all North Americans are deficient in magnesium. Regular daily supplementation to ensure a minimum intake (dietary and supplemental) of about 400 mg/day of elemental magnesium would seem to be in order as an important preventive measure.

Quinolones may increase risk of Achilles tendon rupture

ROTTERDAM, THE NETHERLANDS. Quinolones are broad-spectrum antibiotics often used to treat respiratory tract or urinary tract infections. The most commonly prescribed ones are ofloxacin (Floxin), ciprofloxacin (Cipro), and norploxacin (Noroxin). A team of British and Dutch researchers now reports that quinolone therapy is significantly associated with an increased risk for rupture of the Achilles tendon, particularly among older people and people who are also being treated with corticosteroids at the same time.

Their study is based on information obtained from the General Practice Research Database in the UK

during the period 1988 through to 1998. During the study period there were 1367 reported cases of Achilles tendon rupture (ATR) or about 3.5 to 5.5 per 100,000 person-years depending on age. The use of oral corticosteroids, end-stage renal failure, rheumatoid arthritis, osteoarthritis, gout, systemic lupus erythematosus, polymyalgia rheumatica, ulcerative colitis, diabetes, and Crohn's disease were all found to be significant risk factors for ATR.

The researchers also noted a significant association between quinolone use and ATR. Patients between the ages of 60 and 79 years had a 6-fold increased risk of ATR if using quinolones than did matched controls, and patients over 80 years of age had a 20-fold increase in risk. The risk rose with increased daily dosage and was highest for ofloxacin (28-fold increase) and lowest for ciprofloxacin (3.6-fold increase). The risk also increased significantly with simultaneous use of corticosteroids. The researchers conclude that, although the overall risk of ATR is low, it does increase significantly with age (over 60 years), increasing dose, and concomitant use of corticosteroids.

Van der Linden, Paul D., et al. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. **Archives of Internal Medicine**, *Vol. 163, August 11/25, 2003, pp. 1801-07*

Fish consumption lowers heart rate

LILLE, FRANCE. There is increasing evidence that an elevated heart rate is associated with an increased risk of sudden cardiac death. In the Paris Prospective Study, which included more than 7700 men followed up for 23 years, the mean difference between controls and patients who died suddenly from cardiac arrest was 4.1 beats per minute.

A group of European researchers now reports that regular fish consumption can lower heart rate by as much as 2 bpm. Their study included 9758 men aged 50 to 59 years from four European cities (Belfast, Lille, Strasbourg, and Toulouse). Twenty-seven per cent of the men consumed fish less than once per week, 47% consumed fish once a week, 20% twice a week, and the remaining 6% more than twice a week. The average heart rate (adjusted for age, physical activity, smoking, alcohol consumption, etc) was 67.5 bpm in men consuming fish less than once per week and 65.6 bpm in men consuming fish more than twice per week. Fish consumers also had lower triglyceride levels, lower blood pressure (both systolic and diastolic), and higher levels of beneficial HDL cholesterol than did non-consumers. The erythrocyte content of DHA (docosahexaenoic acid) in the blood was found to be inversely correlated with heart rate.

The researchers point out that there is considerable evidence that omega-3 fatty acids such as those found in fish and fish oils stabilize the electrical activity of heart cells by elevating the action potential threshold and prolonging the relative refractory time. There is also evidence that a high omega-3 content of blood cells and serum cholesterol esters is associated with increased heart rate variability. A higher heart rate variability has been associated with a decreased risk of cardiac disease and a longer lifespan.

Dallongeville, Jean, et al. Fish consumption is associated with lower heart rates. **Circulation**, *Vol. 108, August 19, 2003, pp. 820-25*

Vitamin therapy reduces restenosis after angioplasty

ENCINITAS, CALIFORNIA. Angioplasty (percutaneous coronary intervention or PCI) is used to open up (dilate) coronary arteries so as to produce a more abundant blood supply to the heart. The beneficial effect of angioplasty is, unfortunately, often short-lived with 40% or more of the opened artery segments closing up again (restenosis) within 6 months of the operation.

A team of American researchers now reports that the incidence of restenosis in smaller coronary arteries can be markedly reduced by decreasing homocysteine levels through supplementation with folic acid and vitamins B6 and B12. Their double-blind, randomized clinical trial involved 205 patients who underwent angioplasty to open up small (diameter less than 3 mm) coronary arteries that were at least 50% blocked (stenosis). Half the participants received 1 mg folic acid, 400

micrograms vitamin B12, and 10 mg vitamin B6 on a daily basis while the other half received a placebo. After 28 weeks (plus or minus 6 weeks) 42% of the control group had experienced restenosis as compared to only 15% of the vitamin-treated patients; this is a relative reduction in restenosis rate of 66%. The benefit of homocysteine lowering therapy was highest among patients treated with balloon angioplasty only (82% relative risk reduction) and significantly less in patients who had stents implanted. The benefits were also higher among patients with high levels of low-density lipoprotein cholesterol.

The researchers conclude that homocysteine lowering therapy with vitamins significantly reduces the risk of restenosis in patients treated with PCI for stenosis of small coronary arteries.

Schnyder, Guido, et al. Effect of homocysteine-lowering therapy on restenosis after percutaneous coronary intervention for narrowing in small coronary arteries. **American Journal of Cardiology**, *Vol. 91, May 15, 2003, pp. 1265-69*

Fructose intolerance may be root of bowel problems

IOWA CITY, IOWA. Fructose corn syrup is increasingly used as a sweetener in sodas, fruit juices, and candy, and fructose itself is naturally present in apples, pears, peaches and oranges. Unlike glucose, which is readily absorbed by the body, the capacity for absorbing fructose is limited. Unabsorbed fructose can draw fluid into the small intestine leading to abdominal pain and bloating. Unabsorbed fructose arriving in the large intestine (colon) is likely to ferment with resulting excessive production of hydrogen, methane, and other gases. This again may lead to bloating, flatulence and diarrhea.

Researchers at the University Iowa now report that an inability to absorb fructose (fructose intolerance) may be the root cause of many persistent, unexplained, nonspecific gastrointestinal (GI) problems. Their study involved 183 patients with unexplained, nonspecific GI problems. The most common symptoms among the patients were flatulence, abdominal pain, bloating, belching, and occasional diarrhea. All patients underwent a fructose breath test involving ingestion of 50 g of fructose in 150 ml of water followed by the measurement of hydrogen and methane in the breath. Seventy-three per cent had a positive result indicating the presence of unabsorbed fructose.

In another series of tests 89 patients with unexplained GI problems were given various concentrations of fructose solutions to see if this would reproduce their GI symptoms. The symptoms were reproduced in 88% of patients given a 33% fructose solution (50 g in 150 ml water) and 80% of these patients tested positive in the fructose breath test.

The researchers conclude that a significant proportion of patients with unexplained, nonspecific GI problems may actually suffer from a fructose intolerance. They emphasize that fructose intolerance must be excluded through appropriate testing before patients are assigned the catch-all designation of irritable bowel syndrome. Fructose intolerance is relatively easily managed by simply excluding fructose from the diet whereas irritable bowel syndrome is much more difficult to treat.

Choi, Young K., et al. Fructose intolerance: an under-recognized problem. **American Journal of Gastroenterology**, *Vol. 98, June 2003, pp. 1348-53*

Connection between heart disease and iron questioned

CRAWLEY, WESTERN AUSTRALIA. In 1981 it was proposed that high body stores of iron, more specifically serum ferritin stores, are associated with an increased risk of coronary heart disease (CHD). The iron is believed to help catalyze oxidation reactions that produce free radicals, which in turn lead to increased lipid peroxidation and subsequent CHD. Several studies have supported the hypothesis while others have not. Now researchers at the University of Western Australia weigh in with the results of a new large study that does not support the idea that high iron stores are a risk factor for CHD.

The study involved 1612 men and women who were enrolled in the 1981 Busselton Health Survey and who were free of cardiovascular disease at the time of enrollment. The participants were between the

ages of 40 and 89 years when first joining the survey in 1981. By 1998 217 of the participants had either died from CHD or been admitted to hospital for CHD and 118 had suffered a stroke. Serum ferritin levels were measured in cases and 450 random controls in samples frozen since 1981. There was no indication that higher serum ferritin levels were associated with an increased risk of cardiovascular disease (CHD and stroke).

The researchers conclude that accumulated evidence from prospective studies does not support a connection between iron stores and cardiovascular disease risk, but does support further work in the area, especially studies involving women and studies aimed at investigating interactions/synergies between serum ferritin level and other risk factors.

Knuiman, M.W., et al. Serum ferritin and cardiovascular disease: a 17-year follow-up study in Busselton, Western Australia. **American Journal of Epidemiology**, *Vol. 158, July 15, 2003, pp. 144-49*

Iron supplementation in pregnancy

ADELAIDE, AUSTRALIA. Iron deficiency during pregnancy is quite common as is the more serious condition, iron deficiency anemia. The medical protocol for treating pregnancy-related iron deficiency varies considerably by country with the USA and France recommending routine supplementation with 30-60 mg/day of elemental iron while Australia, Canada, the UK, and New Zealand only recommend supplementation if an iron deficiency is actually diagnosed. Supplementation with high doses of iron can cause nausea and constipation, inhibits the absorption of zinc, and is a common cause of poisoning in early childhood.

Australian researchers now report that routine supplementation with just 20 mg/day of iron in the form of ferrous sulfate is effective in preventing iron deficiency during pregnancy. The randomized, double-blind, placebo-controlled trial involved 386 women who were assigned to receive either an iron supplement or a placebo from week 20 of gestation until delivery. At time of delivery only 3% of the women in the iron group had iron deficiency anemia as compared to 11% in the placebo group. Similarly, only 35% had iron deficiency as such in the iron group as compared to 58% in the placebo group. The benefits of supplementation extended beyond the delivery and termination of supplementation. Six months postpartum only 16% of the women in the iron group had an iron deficiency as compared to 29% in the placebo group. There were no differences in serum zinc concentrations between the two groups and pregnancy outcomes were not different either. All women were screened for iron deficiency anemia at week 28 and those identified as having anemia were placed on high-dose iron supplementation. Eighteen per cent of the women in the 20 mg/day iron supplementation were found to have anemia at week 28 as compared to 30% in the placebo group.

The researchers conclude that supplementing with 20 mg/day of iron from week 20 of gestation until delivery is effective in preventing iron deficiency in pregnant women.

Makrides, Maria, et al. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. **American Journal of Clinical Nutrition**, *Vol. 78, July 2003, pp. 145-53*

Cholesterol protective in older people

LEIDEN, THE NETHERLANDS. There is increasing evidence that while high total and high LDL cholesterol levels are associated with an increased risk of cardiovascular disease in middle age they may actually be protective in old age that is, in people older than 85 years.

Researchers at Leiden University recently completed a study aimed at investigating the association between cholesterol levels and mortality in older people. Their survey involved 561 older people who were followed for 4 years subsequent to their 85th birthday. During the follow-up 152 of the participants died. The leading cause of death was cardiovascular disease, but there was no indication that high LDL levels were associated with an increased risk. Low HDL levels, on the other hand, were associated with a 2-fold higher risk of fatal cardiovascular disease and a 2.6 times higher risk of stroke. Low LDL and HDL levels were both associated with a 2- to 3-fold increased risk of dying from an infection.

The researchers conclude that high cholesterol levels are not a risk factor for cardiovascular disease in old people and that it would make more sense to attempt to increase HDL levels than to lower LDL and total cholesterol levels with statins and other medications. It is important to note that old people with high cholesterol levels (LDL, HDL and total) actually had a lower overall mortality than did those with low levels because of the protection afforded by cholesterol against dying from infectious diseases.

Weverling-Rijnsburger, AWE, et al. High-density versus low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. **Archives of Internal Medicine**, *Vol. 163, July 14, 2003, pp. 1549-54*

NEWSBRIEFS

Vaccination program put on back burner. Plans by the US Government to vaccinate nearly half a million healthcare workers against smallpox have been a dismal flop. So far, less than 39,000 people have actually been vaccinated. The vaccination campaign was part of the general preparation for a bio-terrorist attack. Doctors and nurses refused to be vaccinated with the live virus because they feared that they may spread it and thus harm patients with impaired immunity. Several of the vaccinated military personnel and healthcare workers developed complications including 52 cases of heart inflammation. The smallpox vaccination program has now been put on hold.
New Scientist, August 23, 2003, p. 6

Herb conquers malaria. Researchers at St. George's Hospital Medical School in London, England report that an extract from the Chinese herb qinghao or sweet wormwood (*Artemisia annua*) is effective in the treatment of malaria. The new herbal extract has already helped millions of patients in Southeast Asia who would otherwise have suffered or died when conventional drugs such as chloroquine failed. The extract works by disabling a vital enzyme in the malaria parasite (*Plasmodium flaciparum*) causing it to die within hours. It is expected that improved versions of the extract will cure malaria in 3-4 days.
New Scientist, August 23, 2003, p. 16

Bacteria-powered fuel cells. Researchers at the University of Massachusetts have discovered a new bacterium (*Rhodoferax ferrireducens*) that will eat practically anything and turn it into electricity. The bacterium breaks down sugars by stripping them of electrons, which can then be picked up by an electrode in a fuel cell and generate an electric current. The bacterium is 83% efficient in stripping electrons off sugars and converting them to carbon dioxide and water. It is particularly effective in dealing with xylose, a waste product generated in the manufacture of paper and plans are underway to see if it can be used to clean up paper mill effluents.
New Scientist, September 13, 2003, p. 19

T-rays detect cancer. Terahertz radiation or T-rays is a new form of radiation generated by firing a laser at a semiconductor crystal. The rays are non-ionizing and therefore do not have the health risks inherent in X-rays. Preliminary tests have shown that T-rays clearly pick out skin cancers and melanomas a few millimeters below the surface of the skin and greatly facilitate the job of ensuring that all of the cancer is removed during surgery. The developer of the new technology, TeraView, hopes to ultimately develop a T-ray probe that will be able to scan for cancers of the esophagus and colon as well.
New Scientist, August 30, 2003, p. 11

Polymer lens could replace eyeglasses. Most people over the age of 45 years need reading glasses because the lenses in their eyes have "hardened" and are no longer able to accommodate the change in shape required for close-up viewing. Researchers at the University of New South Wales in Australia now report that they have developed a siloxane-based polymer gel, which could be used to replace the contents of the lens and restore close-up viewing ability. The implantation of the gel would be somewhat similar to cataract surgery. A small incision is made in the cornea, a tiny hole is cut in the lens, and its contents sucked out and replaced with the liquid polymer. The polymer is then cured with UV light. The technique still needs a few years of research before it is likely to become common practice.
New Scientist, August 9, 2003

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

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

TREATMENTS-PRESENTLY APPROVED BY THE FDA

AD is at present incurable, and thus only the treatment of symptoms, both cognitive and behavioral, represents current medical practice (2, 27). The cholinesterase inhibitors are the only class of drug that is currently approved (FDA) to treat AD and cognitive impairment. Motivation comes from the observation that a deficit of acetylcholine occurs in brains of AD patients. Acetylcholine is one of the principal chemical messengers in the body. After it is released into the space between nerves, it is quickly broken down by the enzyme cholinesterase. The cholinesterase inhibitors decrease the activity of this enzyme and are therefore thought to restore to some extent the concentration of acetylcholine in the AD brain.

The use of cholinesterase inhibitors in clinical practice has recently been reviewed by Cummings (108), and as well is discussed in recent books on AD (2, 27). The three commonly used drugs are donepezil (Aricept), rivastigmine (Exelon), and glantamine (Reminyl). They produce reproducible effects in patients with mild-to-moderate AD, with drug-placebo differences seen on global and cognitive measures. Their use is also associated with improvements in activities of daily living and behavior, a delay in nursing home admission, and there is some evidence that they remain effective over several years (108). They do not stop the progression of AD, but they delay the symptoms of cognitive decline. It is considered a success if a patient takes one of these drugs and after two years there has been no further decline (27). One of the most noticeable effects is on behavioral problems and attention (108). Side effects of cholinesterase inhibitors include nausea, vomiting, diarrhea and anorexia. Cholinesterase inhibitors have also been found to provide modest improvements in patients with VaD (108).

Antipsychotic, antianxiety and antidepressant drugs are frequently prescribed to treat behavioral symptoms. These drugs can increase the quality of life for both the patient and caregiver, but they also can have a number of side effects (2).

Some physicians use large doses of vitamin E along with cholinesterase inhibitors, and this appears to be accepted as standard medical practice (6). The justification is primarily from a paper in the April 24, 1997 issue of the *New England Journal of Medicine*, which reported that patients with moderate AD treated with high doses of vitamin E (2000 IU per day of dl-α-tocopherol) experienced on average a 7-month delay in the progression of the disease. This antioxidant delayed the loss of the ability to perform daily activities, the necessity of moving into a nursing home, and the progression to severe dementia, but cognition itself did not improve (109). Large doses of vitamin E should only be taken under a doctor's supervision because of possible side effects such as bleeding and GI problems (2). Studies are currently ongoing regarding the question of the use of cholinesterase inhibitors and/or vitamin E in the treatment of MCI, and the results are awaited with considerable interest.

OTHER APPROACHES TO DECREASING THE RISK OF VaD, AD AND MCI AND SLOWING THE PROGRESSION OF THESE DISEASES

This is perhaps the most exciting area currently under investigation because the question of risk reduction, i.e. primary prevention, is addressed.

REDUCING THE RISK OF VASCULAR DISEASE

Since vascular disease is implicated in the development of dementia, perhaps even starting in mid-life, reducing the associated risk factors should be given high priority, quite apart from the benefits associated with reducing

the risk of heart attack or stroke (27). One obvious approach is to assess, with the assistance of one's physician, the status of the various CVD risk factors. These should include cholesterol and triglyceride levels, i.e. a complete blood lipid profile, blood pressure, weight, homocysteine levels, presence of insulin resistance or diabetes, smoking, and perhaps C-reactive protein and fibrinogen levels. While the direct connection between smoking and AD is controversial, it is nevertheless a risk factor for CVD and cancer. Action in general is indicated if any of the CVD risk factors are outside the normal range. If there is any question at all regarding insulin resistance, a glucose tolerance test seems indicated since fasting glucose alone does not reveal the whole picture. The most common glucose tolerance test involves a fasting glucose followed by a glucose challenge (a drink). Serum glucose is then measured two hours later.

There is an understandable reluctance on the part of many individuals to take prescription drugs unless it is absolutely necessary, and there appears to be great merit in a plan which first attempts to normalize CVD risk factors by aggressive lifestyle changes such as diet and exercise. Since being overweight or obese is very common in the developed world, the question of diet will be important for many individuals. Unfortunately, this requires confronting the controversy concerning low-carb vs. high-carb diets and the question of the role of dietary fat (83). Space does not permit a discussion of this topic, but the reader is referred to Walter Willett's new book (83) and the text and references of the three-part article in the IHN newsletters of November 2002 to January 2003, which is concerned with the relation of diet, and in particular dietary fat, and CVD.

SUPPLEMENTS AND OVER-THE-COUNTER DRUGS

VITAMINS E AND C. Vitamin E is the only supplement (at 2000 IU/day) used by mainstream medicine to treat the progression of AD. However, there has been considerable research regarding the role of vitamin E in reducing the risk of AD and VaD in individuals initially free of dementia (39). The results are not consistent. Recent studies have had as endpoints AD, VaD and cognitive function, with most studies using only one of these outcomes. Both the use of supplements and the intake of dietary vitamin E have been studied, and as well, the concurrent use of vitamin C. In some studies vitamin E from foods was found effective, with no added influence from supplements. This is reminiscent of studies concerned with vitamin E and CHD which also have been inconsistent and where some studies found vitamin E from food rather than supplement sources to be protective.

Vitamin E consists of a number of forms, the most important of which appear to be α-tocopherol and γ-tocopherol. In the North American diet, about 70% of the vitamin E from food sources is said to be γ-tocopherol, supplements are generally d-α-tocopherol, or the synthetic "dl" form. One mg of natural vitamin E is equivalent to approximately 1.5 IU of d-α-tocopherol, whereas 1 mg of the synthetic form is approximately equivalent to 1 IU of dl-α-tocopherol. The α-tocopherol form is regarded as having much higher bioactivity as compared to γ-tocopherol, although this may be an artifact of the measurement of activity. In addition, supplementation with α-tocopherol suppresses both plasma and tissue γ-tocopherol. The α-form and γ-form also do not have identical biological actions, and the γ-form is thought to be a more potent anti-inflammatory agent than the α-form (110). The point of all these details is that food sources are different than supplements and that vitamin E supplements interact with and suppress the γ-form from food. The net result is the *potential* for great confusion and inconsistent results unless these factors are taken into account. However, whether this is the reason why some studies find protective effects with food sources alone is still unclear.

The amount of vitamin E available from food in typically in the range of 5-15 IU which is significantly less than what is generally taken via specific supplements, i.e. 100-800 IU. It is thus fascinating that two recent studies (42, 111) found that vitamin E from food, especially at the high end of >15 IU/day, to be significantly protective for AD, with no added effect of supplements, although these studies did not rule out a role of supplements alone producing a positive result. On the other hand, Grodstein et al in a very recent study from Harvard (112), which was based on a cohort from the Nurses Study, found that the use of specific vitamin E supplements along with specific vitamin C supplements, both at high doses (E > 600 mg/day, C > 750 mg/day), for greater than 10 years was related to modest cognitive benefits in older women (70-79 y of age). For those taking vitamin E alone, the benefits appeared to be weaker and there was no evidence of a trend with duration of use. They also found little support for the effect of vitamin C supplementation alone on cognitive function. Morris et al (113) recently reported that when the endpoint was cognitive decline with age, vitamin E intake from foods or supplements was

protective, but there was no evidence of an association with vitamin C. Studies of vitamin E or vitamin E plus vitamin C status in the plasma or cerebral spinal fluid have also found inverse correlations with the risk of loss of cognitive function (114, 115). Also, Masaki et al (116) found that supplementation with vitamin E and C provided protection against both VaD and cognitive decline, but E alone was not effective.

A number of other studies could be quoted, and while the majority comes out in favor of vitamin E, some find no statistically significant effect. However, it would appear that there is sufficient evidence in connection with reducing the risk of cognitive decline, VaD or AD to justify either supplementation with both E and C, or making sure that ones diet is rich in both. The problem is that it is not easy to get large amounts of E from food (83). Food sources include vegetable oils, whole grains, green leafy vegetables and nuts.

VITAMIN B12, FOLIC ACID AND VITAMIN B6. As discussed above, high serum levels of homocysteine as well as low levels vitamin B12 and folic acid (folate) appear to be significant risk factors for AD, VaD, and cognitive decline. Thus, obtaining serum levels of homocysteine and B 12 as part of a risk assessment or physical exam would appear to be a reasonable step toward prevention. High levels of homocysteine are treated effectively with B 12, B 6 and folic acid. However, the interpretation of serum B 12 levels is not as simple. There appears to be a poor correlation between serum levels and tissue levels, so that serum levels can fail to reveal a deficiency (117). Also, studies that relate serum levels to neuropsychiatric abnormalities or AD have used a variety of cut-off values which go well into the conventional, normal serum range, which suggests that the conventional "normal" cut-off is too low. A realistic cut-off of 300 pg/ml has been suggested (117). In addition, anemia that can be caused by a B 12 deficiency does not in general coexist with the neuropsychiatric abnormalities or AD, and thus the absence of anemia is not relevant in this context, but its presence is, since it is well known that anemia increases the risk of dementia (117).

High homocysteine levels provide a fairly satisfactory marker for low B 12 and folate. Thus there are thus two simple actions indicated. First, if homocysteine levels are high, it seems reasonable that they should be treated aggressively until brought to normal. While many physicians would measure serum B 12 levels in patients presenting with cognitive or memory complaints, there is a problem when the results are "low normal," as well as a problem with above mentioned issue with tissue vs. serum levels. It can be argued that since it is cheap, simple and safe, supplementation with B 12 is indicated in these cases simply to see if it produces an improvement in clinical symptoms. In this context, a recent study by Abyad (117) is interesting in that he found the reversal of clinical symptoms among a group with cognitive dysfunction was most pronounced if they were treated early, with patients returning to normal if treated within three to six months, and poor results when treatment was initiated a year after the appearance of symptoms. This may explain why studies examining the reversal of dementia or cognitive impairment with B 12 therapy frequently yield poor results (118).

Both oral and intramuscular administration has been shown to increase serum levels (119). It would seem that the oral *sublingual* approach is the easiest to implement, although injectable B 12 is available without prescription in some jurisdictions. With the elderly, there can be a serious problem of absorption from oral supplementation, and in fact this may be one of the reasons for the deficiency in the first place. A typical oral dose of 2 mg/day (not sublingual) was found to be as effective as 1 mg intramuscularly per month (119). Some physicians start with more frequent injections. Multivitamins generally contain only very small amounts of B 12. Sublingual oral administration circumvents some of the absorption problems. Food sources of vitamin B 12 include milk products, meat, poultry, fish and spinach. Sources of folate include green leafy vegetables, beans and peas, grain products, tomatoes, oranges, beets, soybeans, fish and eggs.

OMEGA-3 ESSENTIAL FATTY ACIDS AND FISH OIL. The link between AD, VaD and CVD has been discussed. Epidemiologic studies suggest that omega-3 fatty acids reduce the risk of CVD by decreasing the risk of arrhythmias and thrombosis, decreasing triglyceride levels and the rate of growth of atherosclerotic plaque, improving endothelial function, and reducing inflammatory responses (120, 121). The American Heart Association (AHA) (120) recommends that all adults eat fish (in particular fatty fish) at least two times a week. For patients with high levels of triglycerides, the AHA recommends eicosapentaenoic and docosahexaenoic acids (EPA and DHA) supplements, e.g. fish oil, of two to four grams a day. Patients taking more than three grams of these fatty acids from supplements should do so only under the care of a physician. Dietary actions to reduce the risk of CVD have been discussed in detail in many publications (83, 122, 123).

There have been limited peer reviewed reports of intervention studies. Yehuda et al (124) used a mixture of omega-3 and omega-6 fatty acids in a ratio of 1:4 in a 4-week study of 100 AD patients and found improvements in mood, cooperation, appetite, sleep, short term memory and the ability to navigate in the home. Terano et al found a decrease in the severity of AD when subjects were supplemented for one year with 0.72 g DHA/day (125). There is also a case study reported that implicated Omega-3 fatty acids in the reversal of AD. In 1990 an Australian physician, Dr Robert Peers, reported (126) observing a remarkable reversal of AD in a nursing home patient. The patient went from being restless and destructive and unable to dress himself to being calmer, regaining weight and was again able to dress himself. It appeared the reason for this totally unexpected improvement was that fish was served every week, which provided omega-3 fatty acids that had been almost totally absent in the patient's diet for at least five years before he was diagnosed with AD.

There is now additional evidence for the merits of omega-3 fatty acids and in particular fish oil for the treatment of late AD. In the recent book *The Omega Rx Zone* (122), Barry Sears describes the work of Dr. Dan Ward, who owns and operates an extended care and rehabilitation center in Florida. Along with Dr. Sears he developed a protocol for treating terminal AD patients with very high doses of pharmaceutical grade fish oil—25 g/day. Twenty-five grams per day of fish oil is indeed a very high dose, and it is important that the oil be free of dangerous contaminants. The fish oil was combined with a diet based on Sears' *Zone* principles (moderate amounts of complex carbohydrates, low fat protein and monosaturated fat) and fed using shakes that these patients could consume. The results were sensational. Some patients went from being bed ridden and totally unable to take care of themselves to eating normally, playing cards, recognizing friends and family, and even going home to lead more or less normal lives. Ward and Sears observed that the improvement was fish oil dose dependent, indicating that the omega-3 supplementation was probably responsible for the remarkable reversal of what is universally an irreversible decline until death. They also observed a positive, synergistic effect of the altered diet. This is of course the sort of anecdotal evidence that is held is great contempt by those dedicated to the principles of evidence based medicine, but it stretches the imagination to ascribe these results to a placebo effect and suggest that perhaps a proper double blind, placebo controlled study would yield different results. After all, these patients were barely aware of their surroundings! It would be like suggesting that animal studies be placebo controlled! The study of Yehuda et al (69) discussed above provides one possible mechanism for these observations. It remains to be seen if an increase in neuronal membrane fluidity and a restoring of the aging neuronal membrane could be responsible for the action of fish oil in the reversal of late-stage AD.

Thus following the AHA recommendations concerning omega-3 essential fatty acids for cardiovascular health should also have a positive effect on brain health. Food sources of omega-3 oils include fish, walnuts, flaxseeds, canola oil and so-called omega-3 eggs, where the chickens have been fed flaxseed. Fish oil provides the omega-3 fatty acids EPA and DHA, both of which can be made in the body from non-fish sources. However, the ability to synthesize these fatty acids from α-linolenic acid, the omega-3 fatty acid found in, for example, flax seed and nuts, may decline with age. Thus there may be a significant advantage associated with getting the required substances either from fish or fish oil. The pharmaceutical grade of fish oil presumably has much lower levels of impurities than usually found in the ordinary variety. This grade is available over the Internet (http://www.omega3zone.biz/fishoil/).

GINKGO BILOBA. An herbal medicine which appears to enhance blood circulation and has antioxidant properties. Ginkgo has been used extensively in China and Europe for treating a wide range of conditions including memory and concentration problems, confusion, depression, anxiety, tinnitus and headache as well as AD. The mechanisms of action are thought to involve increasing blood supply by dilating blood vessels, reducing blood viscosity, modifying neurotransmitter systems and reducing the levels of oxygen free radicals (127). There have been a number of recent studies, mostly double-blind, placebo-controlled and randomized, which examined the effectiveness of ginkgo on memory problems and delaying the onset of AD. Birks et al (127) have made a detailed and comprehensive review of all the studies that met their standards for inclusion. When clinical global improvement was used as a criterion, benefits from the use of ginkgo were found. Benefits to cognition were also found, as well as benefits associated with activities of daily living and mood and emotional function. They found no significant differences between ginkgo and placebo in the proportion of individuals experiencing adverse effects. Not included in this review was a study reported in 2003 (128) that examined the relationship between the use of ginkgo and other cerebral and peripheral vasotherapeutics and the onset of cognitive impairment. The results obtained after a 7-year follow-up indicated these treatments resulted in a significant drop in the risk of developing AD in elderly women. A recent paper in the JAMA reported negative

results for a memory enhancement trial with normal, healthy subjects (129). This study has been criticized on a number of counts (see (130) and subsequent letters to the editor).

The cellular and molecular mechanisms of the neuroprotective actions of ginkgo still remain largely unproved. One interesting aspect was recently presented in the *Proceedings of the National Academy of Science* (131). This study indicated that ginkgo has an inhibitory effect of Aβ aggregation and as well influences an enzyme involved in the cell death signaling process, both of which could account for a neuroprotective effect.

Ginkgo preparations are of variable potency, and dose dependent studies are limited. Typical doses used in studies range from 40 to over 200mg per day (127). Ginkgo has been shown to increase the risk of bleeding in some people, and it can interact with aspirin, warfarin, and other medications. Thus it appears prudent to use it only under the supervision of a physician (27), especially when large doses are contemplated.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS. It has been known for some time that anti-inflammatory agents appear to provide protection from AD. This observation is directly related to the theory that AD is in part an inflammatory disease (132). This important question has been exhaustively reviewed by the Neuroinflammation Working Group (133), who provide strong arguments for the consideration of AD as an inflammatory disease, even though the relative contribution of inflammation in comparison to other mechanisms of neurodegeneration still remains unclear (132). Non-steroidal anti-inflammatory drugs have received considerable attention in epidemiologic studies related to prevention or delaying onset or progression of AD. Already by 1996, 17 studies had been published and reviewed (134) and a review in 2001 (135) discusses a total of 22 studies. The most recent review was published in 2003 (136). Typically, odds ratios in the range of 0.4 to 0.6 are found for risk reduction associated with NSAID use, although the study based on the Rotterdam Study cohort (12) found an amazing relative risk of developing AD of 0.2 for those taking NSAIDs for more than 24 months. No effect was observed with aspirin, in agreement with most but not all studies, but aspirin was positively associated with the risk of VaD. These studies involve conventional NSAIDs such as ibuprofen, naproxen, and diclofenac, which inhibit both COX-1 and COX-2 activity. It is significant that NSAIDs appear to only offer protection up to a point several years prior to the appearance of diagnosable dementia. Thus their utility appears to be in primary prevention in the early or latent stages of the disease. This is consistent with the fact that to date there are no trials showing a significant slowing of AD progression in groups of patients treated with an anti-inflammatory drug (135). Also, NSAIDs use does not appear to influence the risk of VaD (135). The new COX-2 inhibitors Celebrex and Vioxx are currently being tested for its effectiveness is primary and secondary prevention. It will be several years before the results are available.

Thus the critical question--should an individual start taking NSAIDs to lower the risk of developing AD? While this is no doubt a matter of opinion, Dr. Majid Fotuhi, Harvard professor and Neurology Consultant with the Alzheimer's Disease Research Center, Johns Hopkins Hospital answers "not yet" (27). If one has arthritis and takes NSAIDs anyway, then he points out that there is an added benefit. For anyone who does not need to take these drugs, and does not want to follow his recommendation of waiting for more trials, then consultation with a physician is suggested (27). It of course must be emphasized that this class of drug is well known to have the very serious side effect of inducing gastric bleeding, which is in fact quite common in the elderly taking NSAIDs, and can be serious or even life-threatening. Other side effects include ulcers and possible kidney problems (2). All this has to be balanced against impressive risk reductions in the context of primary prevention and the presence of 22+ studies already reported in the literature.

Unfortunately, it appears that there is very little data from long-term studies on low-dose intervention with NSAIDs where primary prevention of dementia is the endpoint. Nevertheless, there is some indication that for reducing the risk of AD, low doses are as effective as the high doses used to treat arthritic pain (135). Long-term studies of the use of low doses must still address the problem of side effects.

ESTROGEN. Studies regarding use of unopposed estrogen to reduce the risk of AD have been inconsistent and there is still no consensus. Under these circumstances, it has been recommended that women should probably not take estrogen for the sole purpose of delaying the onset of AD (2, 27). It is important to distinguish between unopposed estrogen treatment and so-called hormone replacement treatment (HRT) which involves both estrogen and progestin. Two recently reported studies (137, 138) have found that for postmenopausal women over the age of 65, HRT increased the incidence of dementia and had small adverse effect on global cognitive

function. Effects on MCI did not differ between the treatment and placebo groups. These were large and significant studies, and the conclusion is that the risks of HRT outweigh the benefits, since there are also other negative (and recently much publicized) aspects of HRT associated with cardiovascular disease and cancer.

ALPHA-LIPOIC ACID AND N-ACETYL-L-CYSTEINE (NAC). These two chemicals, available as supplements, have been suggested for use in primary prevention or treatment of AD because of their relationship to glutathione, a potent, highly important, and in fact essential endogenous antioxidant, and because they themselves have antioxidant properties as well as other potential actions. In fact, they are found to increase the levels of glutathione, something that taking oral glutathione directly cannot accomplish to a significant extent. It has been suggested (139) that NAC has potential in the prevention and treatment of age-related mitochondrial neurodegenerative disease. NAC has many other actions which are summarized by Atkins (140). α-lipoic acid is also a powerful antioxidant. Packer calls it a universal or superantioxidant and discusses its uses (141). He regards it as by far the best supplement for increasing glutathione levels, recommending 50 mg twice a day. It has been tested for slowing or arresting the decline of cognitive function in AD (142). Positive results were obtained but the study involved only nine patients. Berkson has presented the full and fascinating story of α-lipoic acid and its many uses in a recent book (143), although AD is not featured. Thus there do not appear to be sufficient studies to allow a judgment on the wisdom of supplementation with either of these two substances in the context of AD, although the reader might wish to review the general arguments provided in the books mentioned as to the potential benefits associated with these supplements. There do not appear to be any long-term studies addressing adverse effects, but α-lipoic acid is licensed in Germany for the treatment of diabetic neuropathy (142). NAC is generally accepted by mainstream medicine for the treatment of liver failure that may results from an acetaminophen (Tylenol) overdose (140).

OTHER ANTIOXIDANTS. If one accepts the theory that oxidative stress is an important risk factor for cognitive impairment, VaD and AD, then having a diet rich in antioxidants would obviously seem to be important. There are a number of antioxidants available from food or in supplemental form that are not included in the above discussion, such as Coenzyme Q 10, a large number of flavonoids and carotenoids, and selenium, which while not in itself an antioxidant, is an essential component in two important antioxidant related enzymes. Space does not permit a detailed discussion, and the reader is referred to Lester Packer's book *The Antioxidant Miracle* (141) for a comprehensive review and guidance on supplementation and doses. Packer has for many years been director of a laboratory devoted to antioxidant research at the University of California at Berkeley. His book contains a detailed discussion of many antioxidants and why they are important, even critical for general health. Attention is directed in particular to his theory regarding the so-called *antioxidant network*, consisting of vitamins C and E, coenzyme Q-10, α-lipoic acid and glutathione, which his research indicates involves critical synergism. Readers may also find the book on vita-nutrients by Atkins to be a valuable resource (140).

DIET. The risk factors discussed above suggest that a diet based on slowly digested carbohydrates, high fiber foods, whole grains, nuts, fruits and vegetables, fish and lean meat and red wine might provide protection against CVD and thus dementia (83, 144). Fruits, especially berries, and green, leafy vegetables provide a wide spectrum of antioxidants. Hu and Willett (123) have recently reviewed the most recent epidemiologic results concerning diet and the prevention of heart disease, which is relevant to the prevention of CVD in general and thus AD and VaD, and a general discussion is also available in Willett's recent book (83).

The possibility that AD is at least partly an inflammatory disease also raises diet issues. Barry Sears deals at length with this subject in *The Omega Rx Zone* (122). He emphasizes the importance of a proper dietary balance of the essential polyunsaturated fatty acids to achieve a non-inflammatory state. This means keeping the omega-3 and omega-6 fatty acids in a ratio that does not favor the production of inflammatory eicosanoids and the related inflammatory hormones. Yehuda (69, 124) has also raised this point. To accomplish this Sears recommends a diet that typically is 1/3 lean meat or fish, and 2/3 fruits and vegetables, with added monosaturated fat, for example from olive oil. To this diet he adds several grams daily of pharmaceutical grade fish oil, giving a diet that is rich in omega-3 essential fatty acids and has a good balance of these two essential fatty acids. Yehuda (69, 124) suggests that the omega-3 to omega-6 ratio should be in about 1 to 4, a value which is consistent with estimates of the ratio in the diets of Stone Age Man, whose genetic profile still by and large controls our metabolism today (122). The emphasis in Sears' program is also on slowly digested fruits and vegetables, since insulin control is also an issue. Bread, pasta, rice, potatoes, carrots and foods high in sugar or of high glycemic index are for example minimized, and trans-fat is avoided. Sears advances arguments that

this diet also minimizes the risk of metabolic syndrome, a risk factor for CVD and thus AD, and may even reverse it. Interested readers should consult his book.

MENTAL ACTIVITY. Maintaining a high level of mental activity may be far from simple, especially if an individual's occupation is dull, repetitive, and offers little or no intellectual stimulation. The post-retirement period also can pose a serious problem, even for those who have had intellectually stimulating occupations, and this situation is aggravated by mandatory retirement. The retired mathematics professor who simply plays golf several times a week may view this as keeping active and a welcome respite from teaching, solving problems and perhaps doing research, but the potential decline in intellectual activity and stimulation could be dramatic. Activities that might help exercise the brain include playing contract or duplicate bridge, becoming active in a chess club, doing hard crossword puzzles, or learning to play a musical instrument, just to pick some obvious post retirement activities that offer more mental stimulation than watching TV or mowing the lawn. Taking courses in night school or in the adult education program of a university, or even online is also a possibility. The opportunity exists to learn a new language, or study some demanding topic such as logic, philosophy, mathematics, some aspects of computer science, etc. There are those who actually get a university degree or even a second degree after retirement just for the pleasure of doing it. Many academics have seen this personally and watched these individuals graduate at 70 or 75 or 80 years of age, clearly in possession of "all their marbles."

CONCLUSIONS

Presumably vascular damage is ongoing, probably from an early age, and therefore taking steps to reduce the risk of CVD is indicated for anyone, independent of the presence or absence of cognitive disease. *It would appear sensible to give CVD prevention a very high priority if the concern is preventing cognitive impairment, AD or VaD*.

MCI is not classified as a disease, and main stream medicine does not recognize any treatment (145). However, three classes of drugs and a few of supplements are currently undergoing large clinical trials to determine if they alleviate the memory problems or delay the progression of MCI to AD. Included are cholinesterase inhibitors, vitamin E, estrogen, COX-2 inhibitors, and ginkgo biloba. It will be several years before any results appear. These studies may fail to yield definitive results because it is necessary to demonstrate clinical improvement when only a moderate cognitive deficit is present, and as mentioned above, a considerable percentage of MCI patients remain stable or revert to normal without intervention. It may also turn out that effective preventive measures must be initiated years before clinical symptoms appear. This further complicates the design and execution of studies. The recommendation of mainstream medicine for those diagnosed with MCI is summed-up by the following quote (146): "Treatment (for MCI) should not be prescribed based on current speculation, but must await confirmation from well designed clinical trials." The impatient are advised to enroll in clinical trials (145), an option that must surely have very limited availability! This advice, while no doubt required under the rules of mainstream medicine, ignores supplements that appear of low risk and may offer benefit, but this is an area where everyone is "on their own." A number of the micro-nutrients discussed are already present in food, and modest increases brought about by supplementation may be associated with minimal risk. Larger doses should be taken only under medical supervision.

Studies addressing primary prevention of MCI, AD or VaD that combine a number of interventions, not just two such as we have seen in the case of vitamin C and E, have apparently never been undertaken and in fact may never occur. It has in fact recently been suggested that the use of multiple antioxidants may have considerable merit (36, 147). For example, if one starts in mid-life taking vitamins E, C, various other antioxidants such as flavonoids and carotenoids, and α-lipoic acid, the B vitamins, as well the omega-3 essential fatty acids EPA and DHA, all from modest supplementation in addition to what is obtained from food, and in addition eats a non-inflammatory heart-healthy diet and attempts to minimize all the CVD risk factors, and in addition perhaps takes low doses of NSAIDs, will this program decrease the risk of MCI or AD or VaD? It might be predicted on the basis of what is already known that the results could be sensational, but a study that covered this extensive a set of interventions, had a large cohort, was multi-center and lasted for 20-30 years, would seem totally unrealistic. Who is going to fund it since there are no prescription drugs involved? Besides, critics would say that if positive benefits were obtained, it would be impossible to determine which interventions were responsible. Also there

would be complaints about the absence of blinding. Those accustomed to a more pragmatic way of viewing things might say, “So what if it works.” However, it is possible that large, ongoing prospective studies may be able to address to some extent the question of multiple actions and lifestyle factors in connection with the risk of MCI, AD or VaD, but it remains to be seen if enough data and statistical power is present to provide guidance, and even if anyone is going to look for such answers.

Interventions that show some benefit for mild AD have been discussed above, but trials by and large have not been carried out that satisfy the requirements of evidence-based medicine. Thus, the only approved or tolerated treatments involve the cholinesterase inhibitors and high-dose vitamin E. At present there are no approved, effective treatments for advanced or end-stage AD aside from behavior modifying drugs. The merits of the intervention discussed above for end-stage AD, i.e. high doses of fish oil and a special diet, derive from anecdotal evidence described in a book many physicians would never read, either because they were unaware of its existence or just on general principles. Perhaps the Sears-Ward protocol will be subjected to a trial, although again there is nothing in it for the pharmaceutical industry. High or even moderate doses of fish oil might even be tried on mild or early AD.

Grounds for some optimism can be found in the huge amount of basic and clinical research currently ongoing which may result in new drugs based in part on a growing understanding of the fundamental causes and mechanisms of dementia, although the almost exclusive fixation on the Amyloid Cascade Hypothesis gives cause for concern. Modern imaging techniques also show great promise in providing both diagnosis and a much-needed means of evaluating potential therapies. Also, there is research on blood and urine markers which may lead to approved tests that could aid in differential diagnosis. However, as emphasized above, MCI, AD and VaD appear to be complex, multifactorial diseases which may start in mid-life, and one should not underestimate the challenges that lie ahead or expect cures or highly effective interventions to be just around the corner.

See Part I for References*

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