INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 140 **SEPTEMBER 2003** **12th YEAR**

Welcome back from what I hope has been a wonderful summer for you and your family. In this issue we continue with Part II of Dr. Ware's invaluable review of our current knowledge of Alzheimer's disease. Dr. Ware discusses the probable causes of AD and will follow this up in the October issue with a review of current strategies for preventing, treating and coping with the disease.

Also in this issue we report on a new treatment for polycystic ovary syndrome, glucosamine and chondroitin alleviates osteoarthritis of the knee, effective cholesterol reduction with diet, and more proof that vitamin C supplementation helps prevent heart disease.

Enjoy!

Yours in health,
Hans Larsen, Editor

September Highlights

LETTERS TO THE EDITOR

Can one overdose on fish oil? What would be the consequences of taking too much over a long period of time?

EL, USA

Editor: *Fish tissue oils (omega-3 oils) are generally considered safe at a daily intake of 10% or less of total calories. At a calorie intake of 2000 cal/day this would correspond to about 20 g/day of fish oil - far more than is generally consumed. It is important though to make certain that your intake of other polyunsaturated oils (omega-6 oils) is balanced with the intake of omega-3.*

Fish liver oils (cod or halibut liver oils), on the other hand, can be highly detrimental if consumed in excess. One tablespoon of cod liver oil contains 13,600 IU of vitamin A. Vitamin A toxicity can occur if taken in excess of 50,000 IU/day for a prolonged period or at lower levels if liver function is impaired.

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I would like to know about the role of ascorbic acid in antibiotic therapy. What is the actual therapeutic dosage of vitamin C for patients who suffer from pregnancy-related anemia?

RG, USA

Editor: *There is some indication that antibiotic therapy may reduce vitamin C levels, so supplementing may be advisable. Pregnancy anemia involves an iron deficiency. Vitamin C helps in iron absorption and 500 mg with the 3 main meals would probably be the optimum daily*

dose unless you have hemochromatosis, in which case you need to consult with your doctor before you take either iron or vitamin C supplements. Some fairly recent research indicates that 20 mg of iron (elemental) from ferrous sulfate is as effective and has fewer side effects than the 100 mg/day usually prescribed for iron deficiency anemia in pregnancy.

ABSTRACTS

Prostate cancer: Risk factors and prevention

UMEAA, SWEDEN. Professor Henrik Gronberg, MD of Umeaa University in Sweden presents an excellent review of current prostate cancer research. It is estimated that over 500,000 new cases of prostate cancer was diagnosed worldwide in the year 2000. The incidence varies widely from less than 2 per 100,000 in China to 137 per 100,000 among African-Americans. It is clear that there is both a genetic and lifestyle factor involved in prostate cancer risk. Japanese men, for example, have a four times greater incidence of prostate cancer if they reside in the USA than if they reside in Japan.

Several studies have found a clear association between the western lifestyle and an increased risk of prostate cancer. A high intake of fat, meat and dairy products has been found to be particularly detrimental. Consuming fried or charcoal-grilled red meat has been clearly associated with increased risk. A high intake of alpha-linolenic acid and calcium from dairy products has both been associated with higher risk. A Swedish study found that men who consumed 600 mg/day of calcium from dairy products had a 32% greater risk than those consuming 150 mg/day or less.

Smoking, degree of physical activity, and alcohol consumption have not been associated with an increased risk and neither has vasectomy.

Soybean products (soy milk or tofu) have been found to have a preventive effect as has a high intake of tomato products, lycopene, selenium, and vitamin E. Supplementation with selenium reduced risk by 66% in one study while vitamin E supplementation lowered it by 40%. A large study involving 32,400 men is currently underway to confirm the benefits of vitamin E and selenium supplementation. Results are expected by 2013.
Gronberg, Henrik. Prostate cancer epidemiology. **The Lancet**, *Vol. 361, March 8, 2003, pp. 859-64*

New treatment for polycystic ovary syndrome

ATHENS, GREECE. Polycystic ovary syndrome (PCOS) affects an estimated 3.5-5.0 million women in the United States. PCOS is characterized by irregular or absent periods, abnormal bleeding, infertility, obesity, hair loss, and acne. Its main anatomical feature is enlarged ovaries with an increased number of follicles around the periphery.

The traditional treatment for PCOS involves the use of oral contraceptive pills. An international group of researchers are now questioning this therapy. They point out that PCOS patients are at high risk for developing insulin resistance, glucose intolerance, and heart disease and that these disorders may actually be more common among oral contraceptive users than among non-users. Thus, while oral contraceptives may provide some short-term relief, they could have unfortunate long-term consequences for PCOS patients.

The researchers point out that PCOS patients are insulin resistant and thus at greater risk for diabetes. They reason that drugs which retard the progression from insulin resistance to type 2 diabetes (metformin, troglitazone) may also work in the treatment of PCOS. They would be particularly appropriate in women with other risk factors for diabetes. The researchers also suggest that insulin resistance can be diminished effectively by a combination of diet and exercise.

Diamanti-Kandarakis, Evanthia, et al. A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. **Journal of Clinical Endocrinology & Metabolism**, *Vol. 88, May 2003, pp. 1927-32*

Editor's comment: Animal experiments have shown that supplementation with alpha-lipoic acid is highly effective in decreasing insulin resistance.

Fibrinogen levels linked to cardiovascular disease

NAPLES, ITALY. Japanese researchers have reported that high levels of the blood coagulation factor fibrinogen are associated with an increased risk of premature death from cardiovascular disease and cancer.

Fibrinogen levels are known to be elevated in people with heart abnormalities such as left ventricular dysfunction and elevated arterial stiffness; they also tend to be higher in people with diabetes, obese people and smokers. What is not known is whether high fibrinogen levels on their own, that is, independent of the correlation with other risk factors, are a risk factor for cardiovascular events (heart attack, stroke, sudden death, heart failure, and coronary heart disease).

A team of American and Italian researchers now provides the answer to this question. Their study involved 2671 American Indians without overt coronary artery disease who, after an initial medical examination, were followed for 5 years. During this time there were 158 cardiovascular events, 64 of which were fatal. The researchers observed a 68% increased risk of a cardiovascular event and a 104% increased risk of fatal event in study participants with a fibrinogen level above 400 mg/dL as compared to those with a level below 400 mg/dL. This risk increase was independent of the presence of heart abnormalities and other traditional risk factors such as diabetes, obesity, and smoking. Participants with heart abnormalities (as determined on echocardiograms) and elevated fibrinogen levels were 4 times more likely to have a cardiovascular event and 8 times more likely to die from such an event than were participants with no heart abnormalities and low fibrinogen levels.

The researchers conclude that an elevated fibrinogen level is an independent risk factor for cardiovascular events, both fatal and non-fatal.

Palmieri, Vittorio, et al. Relation of fibrinogen to cardiovascular events is independent of preclinical cardiovascular disease: the Strong Heart Study. **American Heart Journal**, *Vol. 145, March 2003, pp. 467-74*

Editor's comment: Fibrinogen levels can be reduced by increasing daily water intake, by fish oil supplementation or by supplementing with relatively large doses of niacin (1500 mg twice daily).

Homocysteine reduction with folic acid

WAGENINGEN, THE NETHERLANDS. There is growing evidence that a high blood level of the amino acid homocysteine is associated with an increased risk for heart attack, stroke, atherosclerosis, Raynaud's phenomenon, and Alzheimer's disease. Folic acid is known to reduce homocysteine levels and is also effective in preventing neural tube defects. However, it has not been clearly established exactly how much folic acid is needed on a daily basis in order to achieve maximum homocysteine reduction.

Researchers at Wageningen University now report that a daily intake of 400 micrograms of folic acid will reduce homocysteine levels by an average of about 22%. The clinical trial involved 308 Dutch men and women between the ages of 50 and 75 years. The participants were randomized to receive a placebo or 50, 100, 200, 400, 600 or 800 mcg/day of folic acid for a 12-week period. At the end of the trial homocysteine concentrations had dropped by about 10% in the groups receiving 50 or 100 mcg/day, by 22% in the 400 mcg/day group, and by about 25% in the groups receiving 600 and 800 mcg/day. The researchers conclude that about 90% of the maximum homocysteine reduction obtainable through folic acid supplementation can be achieved by supplementing with 400 micrograms daily.

van Oort, Floor VA, et al. Folic acid and reduction of plasma homocysteine concentrations in older adults: a dose-response study. **American Journal of Clinical Nutrition**, *Vol. 77, May 2003, pp. 1318-23*

Glucosamine and chondroitin in knee osteoarthritis

LIEGE, BELGIUM. Osteoarthritis of the knee is a painful, progressive, fairly common disorder among the elderly. Supplementation with glucosamine sulfate and chondroitin, both natural components of healthy cartilage, has long been advocated by natural health practitioners as an effective therapy for osteoarthritis. The medical community, however, has been slow to acknowledge the beneficial effects of these two natural (non-patentable) compounds. This may now be about to change.

Belgian medical researchers have just released the results of a meta-analysis of 15 randomized, placebo-controlled studies involving 1020 patients treated with glucosamine and 755 treated with chondroitin. One of the main symptoms of osteoarthritis is a reduction in the joint space between the bony parts of the knee resulting in pain and eventual erosion of the bone. The researchers found that treatment with 1500 mg/day of glucosamine sulfate for 3 years resulted in a 0.27 mm smaller decrease (narrowing) in joint space than did treatment with a placebo. Pain was also found to be significantly decreased in patients supplementing with glucosamine or chondroitin. Both were well tolerated.

The researchers conclude that daily oral supplementation with glucosamine sulfate slows the degenerative process of joint cartilage and that oral supplementation with glucosamine or chondroitin significantly decreases the symptoms (pain and joint immobility) in patients with osteoarthritis of the knee. The beneficial effects of the two compounds are often felt within 2 weeks of the start of supplementation.

Richy, Florent, et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. **Archives of Internal Medicine**, *Vol. 163, July 14, 2003, pp. 1514-22*

The brain and carbohydrates

SWANSEA, UNITED KINGDOM. The human brain requires glucose and oxygen in order to function. During rest the brain accounts for 20% of the body's energy consumption even though it comprises only 2% of total body weight. Recent studies using position emission tomography (PET scan) has shown that increased mental activity is associated with increased glucose metabolism and that the glucose goes directly to the areas of the brain involved in the mental activity at hand. Researchers at the University of Wales provide a review of the effect of carbohydrates on memory and mood. Among the highlights of their findings:

- Memory processing by the hippocampus may be limited by glucose availability.
- A plentiful glucose supply improves memory possibly because glucose increases the synthesis of the neurotransmitter acetylcholine.
- Low glycemic index foods improve memory more than high glycemic index foods.
- Missing breakfast results in poorer memory performance during the morning.
- A low carbohydrate diet is associated with increased depression, anger and tension over the long term.
- People with better glucose tolerance have better mood and memory. Better glucose tolerance is associated with a rapid fall in blood glucose levels after ingestion of a glucose drink.

The researchers conclude that the nature and timing of meals and snacks can influence psychological functioning and that the glycemic load of the diet has a direct impact on mood and memory.

Benton, David and Nabb, Samantha. Carbohydrate, memory, and mood. **Nutrition Reviews**, *Vol. 61, May 2003, pp. S61-S67*

Chronic fatigue syndrome recognized as major health problem

ATLANTA, GEORGIA. Chronic fatigue syndrome is characterized by an overwhelming fatigue (lasting 6 months or longer) that is not alleviated by rest and interferes substantially with work, education, social or personal activities. Chronic fatigue syndrome was only recognized as a valid medical diagnosis in 1994 and estimates of its prevalence vary from 2.3 to 600 per 100,000 persons.

Researchers at the Centers for Disease Control and Prevention now report a prevalence of 235 per 100,000 persons in a typical US population (Wichita, Kansas). The prevalence was found to be considerably higher among women (373 per 100,000) than among men (83 per 100,000). The prevalence of 373 per 100,000 among women compares to about 1000 per 100,000 for breast cancer and 100 per 100,000 for cervical cancer. Its prevalence peaked between the ages of 50 and 59 years. The incidence (new cases diagnosed in a year) of chronic fatigue syndrome was 180 per 100,000 persons. The researchers conclude that chronic fatigue syndrome constitutes a major public health problem.

Reyes, Michele, et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. **Archives of Internal Medicine**, *Vol. 163, July 14, 2003, pp. 1530-36*

Effective cholesterol reduction with dietary changes

TORONTO, CANADA. A reduction in the intake of saturated fat (less than 7% of total energy intake) and cholesterol (less than 200 mg/day) is usually the first step in the battle against high cholesterol levels. The effect of these changes, unfortunately, is rather small with an expected reduction in low-density lipoprotein cholesterol (LDL) between 4 and 13%. Adding statin drugs (lovastatin, pravastatin, simvastatin, etc.) to this diet (STEP II diet) can increase the reduction in LDL to between 28 and 35%. Statin drugs are, however, by no means free of adverse effects, so many people now prefer other means of cholesterol reduction.

It is well established that viscous fiber, plant sterols, soy products, and almonds all help reduce LDL cholesterol levels. Medical researchers at St. Michael's Hospital now report that including all these items in the standard STEP II cholesterol reduction diet is just as effective as adding statin medications. Their randomized, double-blind, placebo-controlled clinical trial involved 25 men and 21 postmenopausal women with high LDL levels (higher than 158 mg/dL or 4.1 mmol/L). The participants were randomized to eat just the STEP II diet plus a placebo capsule, the STEP II diet plus a capsule containing 20 mg of lovastatin or the STEP II diet with added plant sterols (1.0 g per 1000 kcal) in the form of a plant sterol ester-enriched margarine, viscous fiber (9.8 g per 1000 kcal) from oats, barley and psyllium, soy protein (21.4 g per 1000 kcal) as soy milk or meat substitutes, 14 g of almonds per 1000 kcal of diet plus a placebo capsule.

After 4 weeks the LDL level in the control group (STEP II diet + placebo) was down by 8%, the LDL/HDL ratio up by 3%, and the level of C-reactive protein down by 10%. In the statin group LDL level dropped by 30.9%, the LDL/HDL ratio by 28.4%, and the C-reactive protein by 33.3%. In the enhanced diet group (STEP II diet + placebo + plant sterols, etc.) the LDL level dropped by 28.6%, the LDL/HDL ratio by 23.5%, and the C-reactive protein level by 28.2%. The researchers conclude that the enhanced diet is just as effective as statin drugs in reducing LDL cholesterol and C-reactive protein levels. The benefits of the enhanced diet were evident within 2 weeks of starting it. They also point out that the estimated reduction in the risk of coronary heart disease was similar in the statin group (25.8%) and the enhanced diet group (24.9%).

Jenkins, David J.A., et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. **Journal of the American Medical Association**, *Vol. 290, July 23/30, 2003, pp. 502-10*

NEWSBRIEFS

Folic acid and multiple births. Folic acid supplementation in women of childbearing age is becoming increasingly popular as an effective means of preventing neural tube defects in their offspring. At least three studies have indicated the possibility that supplementation may be associated with an increased incidence of multiple births (twins or triplets). A major study in China questions this association. Over 242,000 women were randomized to receive a placebo or 400 mcg/day of folic acid prior to conception and during pregnancy. The Chinese researchers found no difference in the number of multiple births between the two groups, but actually noted a lower incidence of multiple births in women who took folic acid (0.59%) than in women who did not (0.65%).
The Lancet, Vol. 361, February 1, 2003, pp. 380-84

Vitamin C helps prevent CHD. A major study involving over 85,000 female nurses found that supplementing with vitamin C helps prevent coronary heart disease. The nurses were followed for 16 years during which time 1356 of them had a nonfatal heart attack (myocardial infarction) or died from CHD. Nurses who supplemented with vitamin C had a 28% lower risk of CHD than did non-users of vitamin C supplements after adjusting for age, smoking and a variety of other CHD risk factors. A high intake of vitamin C from the diet (excluding supplements) was not significantly associated with a lower incidence of CHD.
Journal of the American College of Cardiology, Vol. 42, July 16, 2003, pp. 246-52

Hypertension prevalence in North America and Europe. Medical researchers have just completed a major study of the extent of hypertension among the populations of North America and 6 European countries (England, Finland, Germany, Italy, Spain and Sweden). The study involved over 80,000 people between the ages of 35 and 74 years. Hypertension was defined as a systolic blood pressure over 140 mm Hg or a diastolic blood pressure above 90 mm Hg. The researchers found a prevalence in North America of 27.6% as compared to 44.2% in Europe. Germany had the highest prevalence at 55.3% while Canada had the lowest at 27.4%. The average blood pressure was 136/83 mm Hg in Europe and 127/77 in Canada and the USA. The mortality rate from stroke was found to correlate well with the prevalence of hypertension being 41.2 per 100,000 persons in Europe versus 27.6 per 100,000 in North America. The use of anti-hypertensive medication was significantly lower in Europe than in the USA and Canada.
Journal of the American Medical Association, Vol. 289, May 14, 2003, pp. 2363-69

Nicotine patch ineffective. Finding effective ways of making smokers quit is a real challenge. Researchers at the University of Oxford carried out a randomized clinical trial of the nicotine patch in 1991-92 and found that only 9% of the 1686 study participants had been able to abstain from smoking for one full year. Follow-up 8 years later revealed that only 5% of the original participants had been abstinent for 8 years. Another 7% had quit on their own during the 8 years leaving 88% of the original study participants still smoking. There was no statistically significant difference in abstinence rate between nicotine patch and placebo users.
British Medical Journal, Vol. 327, July 5, 2003, pp. 28-29

Swimming pools and asthma. Nitrogen trichloride is the gas that gives indoor swimming pools their distinctive odour; it is formed when chlorine used to disinfect the water reacts with components of sweat and urine. Belgian researchers now report that exposing children to nitrogen trichloride markedly increases their risk of developing asthma. They also found that the younger the children were when they began swimming the more likely they were to have asthma. Swimming pools with low ceilings were particularly unhealthy. The researchers point out that using ultraviolet light or ozone to sterilize the water would help eliminate the problem of nitrogen trichloride formation.
New Scientist, June 7, 2003, p. 9

Hand-held scanner for cancer. Researchers at the University of Bologna have developed a hand-held scanner, similar to those used in airports, which can be used to detect cancer. Apparently cancer tumours create a strong interference at 400 mega hertz when exposed to a weak microwave field emitted by the scanner. Preliminary trials have shown that the scanner can detect prostate cancer with an accuracy of 93% and breast cancer with an accuracy of 66%. Trials for lung, stomach, liver, and colorectal cancers are underway and it is hoped that the

scanner can be made commercially available later this year.
New Scientist, June 14, 2003, p. 15

Lemon balm for Alzheimer's disease. Researchers at the Tehran University of Medical Sciences report that lemon balm extract (*Melissa officinalis*) is highly effective in improving memory, attention and problem-solving in Alzheimer's patients. Dr. George Wake of the University of Newcastle-upon-Tyne says that the observations made by the Iranian researchers echo those made by his own team. The Newcastle group found that both sage (*Salvia officinalis*) and lemon balm improve memory and boost the activity of the key neurotransmitter, acetylcholine, in the brain.
New Scientist, June 28, 2003, p. 20

Depression may be in the genes. British researchers have found that whether or not an individual becomes depressed after experiencing a number of stressful events depends on the version of a gene involved in serotonin regulation. This gene apparently comes in both a short and a long version. People with two copies of the long version are less likely to get depressed no matter how many stressful events they are exposed to while those with two copies of the short version are much more likely to become depressed. The researchers estimate that 30% of people have two long genes, 50% have a short and a long one, and 20% have two short ones.
New Scientist, July 26, 2003, p. 15

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

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

RISK FACTORS

The following is not a complete list, but it includes the major factors that are thought to increase the risk of dementia. Not included is MCI (mild cognitive impairment), which is discussed in Part I. The risk factors discussed below are for the most part related to what are thought to be the probable causes of MCI, VaD (vascular dementia) and AD (Alzheimer's disease), and in fact illustrate the basis for believing that these dementias have a complex and multifactorial etiology. Many of the risk factors lead to preventive actions, which will be discussed in a later section of this review.

AGE. There is no doubt that after 65 the risk of AD, VaD or mixed dementia increases dramatically. Advancing age should provoke concern regarding prevention.

GENETICS. A risk factor that obviously cannot be changed. There are in fact a number of genetic mutations that appear to favor AD, and in particular early onset AD. The genetic characteristic described by having the APOE allele ε4 (an allele is any one of a series of two or more different genes that may occupy the same locus on a specific chromosome) is implicated in sporadic or late onset AD. Knowledge of the presence of genetic risk factors might lead one to be more aggressive in taking preventive measures. However, current medical practice (27) does not recommend genetic testing. There can be serious psychological issues involved as well as insurance problems (especially in the US). In some cases, an indication of genetic risk is obtained from the presence of early onset dementia in a family.

HEAD INJURY. Well characterized among boxers, where the end result is known as *Dementia Pugilistica.* Head injury with and without the loss of consciousness has in general been found to contribute to the development of AD (34, 35), with the loss of consciousness associated with the highest risk. There is some evidence that head injuries in young men are associated with AD and other dementias in later life.

OXIDATIVE STRESS, VITAMIN DEFICIENCY, POOR DIET, AND LOW ANTIOXIDENT LEVELS. A number of studies suggest that oxidative stress may play a role in the pathogenesis of AD (36). Lesions are

found in AD brains that are typically associated with exposure to free radicals (37). Free radicals, which are highly reactive molecules, inflict damage on cell components and alter chemical components and reactions of biochemical systems, frequently adversely. Also higher intake or higher serum concentrations of some antioxidants are related to reduced risk of AD or cognitive impairment. Antioxidants studied include vitamin E, C, A and those found in red wine (38). Martin and Mayer have recently reviewed studies concerning vitamin E and C and the reduction of the risk of AD (39). This will be discussed in more detail below. The situation with the B vitamins (see below for more details) is more complex because of the relationship with serum levels of homocysteine, an independent risk factor for AD (40). As one ages, the ability to utilize the vitamin content of food may decrease. The nutritional status of the elderly (and others, for that matter) is also frequently poor due to an inadequate diet, which is a common problem among the elderly (41). Related to both of these factors are the commonly observed low levels of antioxidants in the elderly which have been associated with increased risk of dementia (42).

ATHEROSCLEROSIS, EXISTING CARDIOVASCULAR DISEASE, TENDENCY FOR THROMBOSIS. One of the arguments for a vascular component in the etiology of AD and MCI is the epidemiologic observation that the presence of cardiovascular disease (CVD) is a risk factor (18). Also, the presence of atherosclerosis is not only a risk factor for CVD but also for AD (43). Thus individuals having or being at risk of having CVD should be particular aggressive in attempting to decrease or eliminate the CVD risk factors. Factors include hypertension, diabetes, metabolic syndrome (also called Syndrome X), being overweight, having a bad blood lipid profile, and having high C-reactive protein levels.

INSULIN RESISTANCE AND TYPE 2 DIABETES. Both are well known risk factors for CVD and thus, if one believes the connection between AD and vascular disease, they automatically become risk factors for AD and VaD. In addition, there is considerable evidence concerning the effect of insulin and glucose levels on brain health, and there is also independent evidence, based on a number of studies, some with very large cohorts, that type 2 diabetes is a risk factor for cognitive impairment, AD and VaD (44-49). Impaired glucose tolerance is also implicated in poor memory performance in the elderly. (48). Chronically low levels of blood glucose can result in permanent damage to brain cells (19). Chronically high levels of blood glucose imply diabetes.

SERUM CHOLESTEROL. Cholesterol has become the focus of intense interest in connection with MCI and AD, partly due to the recognition that the APOE allele ε4, a known AD risk factor, is involved in cholesterol metabolism (50), and partly because of the epidemiologic evidence that cholesterol lowering drugs decrease the risk of AD (51, 52). Fundamental questions regarding the pathogenesis of AD include how nontoxic, soluble Aβ is converted into its toxic, aggregated form and how the protein tau is hyperphosphorylated to form neurofibrillary tangles. Growing evidence suggests that altered neuronal cholesterol metabolism may be involved in these pathological processes (50). There is also evidence suggesting that the development of late-life AD or MCI is associated with mid-life hypercholesterolemia (high cholesterol levels) (53, 54). The biochemical and pathological details are far from understood, and while the conventional wisdom holds that cholesterol does not cross the blood-brain barrier, there remains the observation that high serum cholesterol is a risk factor for AD (55). In fact, it is thought that brain cholesterol is made in the brain and not derived from the peripheral circulation. Not only statins but other cholesterol lowering drugs appear to decrease the risk of AD, and there are large differences among statins themselves as to their ability to penetrate the blood-brain-barrier (55). Thus, in spite of what appears to be a very primitive understanding of the role and biochemical mechanisms linking cholesterol and dementia, it would appear wise to treat elevated serum cholesterol levels as a significant risk factor.

ELEVATED HOMOCYSTEINE. Again, we see the connection between CVD and AD illustrated in the observation that elevated homocysteine levels are an independent risk factor for AD and dementia (40). This risk factor is closely related to vitamin B12 and folic acid deficiencies. It can be argued that every adult should have their homocysteine blood level measured, and this appears especially true for the elderly. For example, a level greater than 14 micromol/L nearly doubles the risk of AD in the elderly (40). An elevated level calls for aggressive treatment with B vitamins.

VITAMIN B 12 AND FOLIC ACID (FOLATE). Over the years, a number of studies, but not all have indicated that deficiencies in vitamin B12, B6 and folic acid are related to elevated risk of dementia or AD

(56-59). Several recent studies appear to confirm this. Wang et al (60) found in a longitudinal study that the risk increased by two-fold when a serum cut-off of B12 < 150 pmol/L and folate < 10 nmol/L was compared to normal levels of both vitamins. An interesting three-fold increase in risk was found for a subgroup with good baseline cognition, and a similar pattern was seen with higher cut-off of 250 pmol/L and 12 nmol/L. Similar results were found by Clarke et al (61) in a case-control study of total serum homocysteine, B 12 and folate and AD. For folate and B 12 serum levels the odds ratios obtained by comparing the upper with the lower third of the population were 3.3 and 4.3, respectively. Snowdon et al (62) found in the Nun Study that low serum folate was strongly associated with atrophy of the cerebral cortex, particularly in persons with AD lesions seen at autopsy. These results, when considered with a number of other studies (see (60) for references), suggest a strong link to AD risk from low B 12 and folate and high homocysteine, the latter, as discussed above, being also an independent risk factor for AD. However, mechanistic details are far from clear since there are a number of potential ways in which low levels of vitamin B 12 could, for example, lead to decreased cognition and AD (63), and in fact, there may be multiple pathogenic mechanisms at work (40, 64). Thus monitoring the serum B12 and folate concentration in the elderly appears important (60).

DEFICIENCY IN OMEGA-3 ESSENTIAL FATTY ACIDS. Recent studies (65, 66) have provided evidence that a deficiency in the omega-3 essential fatty acids may be linked to the risk of developing AD and other dementias. Correlations were found between risk and plasma levels of these fatty acids. One omega-3 fatty acid in particular, docosahexaenoic acid (DHA), appeared critical, and in another study a low level was not only characteristic of AD patients but also those with cognitive impairment (65). Tully et al used cholesteryl ester-docosahexaenoic acid levels to examine the relationship between DHA levels and AD and found similar results (67). In the Rotterdam Study it was found that low levels of fish consumption, a good measure of omega-3 fatty acid intake, was a risk factor for subsequent development of AD in the elderly (68).

In a recent article in *Neurobiology of Aging*, Yehuda et al (69) describe their recent work on the role of polyunsaturated fatty acids in restoring the aging neuronal membrane. They found that low omega-3 along with high omega-6 levels of fatty acids played a role in free radical damage in the brain, resulting in decreased fluidity of the neuronal membrane, and suggesting that dietary changes could perhaps overcome this problem. In their opinion, the dietary ratio omega-6 to omega-3 should be about 4, which is much lower than that found in most North Americans diets.

HYPOTENSION. A reduction in the blood supply to the brain (hypoperfusion) can adversely effect the supply of both oxygen and nutrients to the brain and lead to permanent damage. Closely related to hypoperfusion is hypotension (abnormally low blood pressure). The association of cerebral hypoperfusion and AD is well established, and recent observations suggest reduced cerebral blood flow is rather global in AD, without significant variation between different brain regions (70). In AD it has also been found that cerebral hypoprofusion is associated with cortical watershed microinfarcts (occlusion in the area where the blood supply from cerebral arteries overlaps at the extreme periphery of the vascular bed) which appear to further aggravate the degenerative process and impact adversely on the risk of dementia (70). Thus monitoring blood pressure and identifying arterial hypotension is very important. In older patients with heart failure, systolic hypotension is also associated with cognitive impairment (71).

HYPERTENSION. Studies concerning the connection between hypertension and dementia are inconsistent (72-74). The reasons appear complex (75) and may be associated with differences in study design, subject selection, etc. Nevertheless, there are a number of studies that find a connection between hypertension and impaired cognition in a broad range of areas (72). In addition, studies have shown a link between midlife hypertension and subsequent development of cognitive impairment (72, 76). It is also hard to ignore the results of intervention trials (77, 78) with antihypertensive drugs, where reductions in the incidence of dementia were observed. In one large, recent study (77), the reduction in the incidence of dementia was found to be over 50%! In this study, patients at entry had systolic pressure between 160 and 219 mm Hg, with diastolic below 95. Treatment consisted of a calcium channel blocker with the possible addition of an ACE inhibitor and/or a diuretic, and the follow-up lasted 2 years (blinded) and almost 4 years overall. The decreases in blood pressure, however, were not particularly large. The authors comment that calcium channel blockers may provide better protection against stroke than diuretics or β-blockers, an effect seen in

other studies. Again, we see a connection between the risk of AD and vascular disease. However, as pointed out above, these medications may have actions related to the risk of dementia that are independent of their effect on hypertension. Obviously, much remains to be clarified.

ALCOHOL ABUSE. The risk curve for the relationship between alcohol consumption and dementia appears to be J-shaped, with many studies indicating a protective effect of moderate consumption, slight risk with abstention, and a high risk associated with alcohol abuse (79-81). In the Copenhagen City Heart Study (82) red wine was found to be the effective drink. The same J-shaped relationship and protective effect is seen in connection with cardiovascular disease (83). Most studies indicate the optimum level of consumption to be one drink (e.g. a glass of wine) a day for women and two for men, but this action can naturally only be recommended if there is no history or risk of alcoholism (83).

ATRIAL FIBRILLATION. Atrial fibrillation is thought to be a vascular risk factor for dementia (84) and may impact the aging brain by sustained hypoperfusion (impaired blood supply). Ott et al (85) using data from the Rotterdam Study, found a significant positive association with both dementia and impaired cognitive function and the presence of atrial fibrillation (risk ratios of 2.3 and 1.7 respectively). The strongest association was with AD rather than VaD. Sabatini et al (86) report an even higher risk ratio of 3.4. Atrial fibrillation has also been identified as an independent determinant of low cognitive function (87).

LEADING DULL LIFE AND/OR A LOW LEVEL OF EDUCATION. This is called the "brain reserve hypothesis" and assumes that the more highly developed and active the brain, the more it is able to tolerate the degenerative processes that occur during aging and the development of MCI, AD and VaD. For example, three recent studies found that in elderly subjects cognitively stimulating activities resulted in a reduced risk of AD or an improvement in cognitive abilities (88-90). Friedland et al (91) also found similar results but comment that it is not clear if mental inactivity is a risk factor or a reflection of very early subclinical effects of AD. There is some evidence that the nature of an individual's lifetime principal occupation is related to the risk of AD (92). In this study, non-manual work was compared with manual or "goods production" work, with the latter yielding an increased relative risk of 1.6. In the famous Nun Study (93), Snowdon and associates found that low linguistic ability in early life (late-teens) correlated strongly with neuropathological assessment of AD at autopsy. They suggest that low linguistic ability may reflect suboptimal neurological and cognitive development, which might then increase the susceptibility to AD pathology in late life. While not all studies confirm the brain reserve hypothesis, and some studies lead to only modest associations (94), it can be argued that in order to 'play it safe" it may be wise to keep the brain as active as possible throughout life and in particular in later life.

ALUMINUM. The hypothesis that aluminum is associated with the risk of AD was proposed over 35 years ago and to this day remains highly controversial. The possible connection between aluminum in drinking water and AD has been the subject of a number of studies with inconsistent results. Recently Gauthier et al (95) proposed that one reason for the many conflicting results is that not enough attention has been paid to the chemical form of the dissolved aluminum. They found that there was a correlation between AD risk and monomeric organic aluminum but not total aluminum in drinking water. However, in a study published in 2000, Rondeau et al found a relative risk of almost 2 for drinking water containing greater than 0.1 mg/L (96). Newman (97) has advanced the hypothesis that an unfavorable ratio of essential fatty acids to total saturated fat plus trans fats may have an adverse effect on the permeability of the blood-brain-barrier, with the result that there can be excessive aluminum accumulation. There is considerable literature on proposed mechanisms of neurotoxicity of aluminum in the brain based on animal and cell culture studies (96, 98).

EMOTIONAL STRESS. The connection between stress and AD appears to properly belong in the relatively new field of psychoneuroimmunology. Dr. Gabor Maté has in fact just published a book, *When The Body Says No*, which provides an extensive discussion of the connection between stress and disease, including AD, and a general introduction to psychoneuroimmunology (99). The mechanisms involved appear to be somewhat speculative, but essentially involve the action of stress on the immune system which generates inflammation with an inappropriate production of interlukin-6 and other proinflammatory cytokines. When this is chronic rather than a short-term "fight or flight" reaction, problems can arise. This chronic immune system dysfunction results in processes in the brain that may ultimately result in damage. It is significant that many markers of these processes are seen in the AD brain (100, 101). While some scientists like to refer to this

as an autoimmune process, it has been suggested that a more appropriate term is *autotoxicity*. The proposed role of autotoxicity in AD has recently been reviewed by McGeer and McGeer (101).

MERCURY. Mercury has been suggested in the etiology of AD, and some individuals have had their mercury amalgams removed. Mercury is of course a well known neurotoxin, but the toxicity appears to depend on exposure and the chemical nature of the mercury. Normal environmental exposure is thought to result in blood levels well below those required for chronic or acute neurotoxicity (102). There appears to be a positive correlation between blood mercury levels and the risk of AD (102), and it is also clear that dental amalgams emit measurable quantities of mercury vapor (103). However, in a landmark paper Saxe et al (104) found no correlation between the number or size of dental amalgams and the mercury load of the brain nor was there any correlation between the incidence of very carefully diagnosed and documented AD and brain mercury levels. The authors conclude that their results do not support the hypothesis that low levels of mercury are a pathogenic factor in AD or that dental amalgams are a major health risk for AD. Nevertheless, there are a number of unanswered questions regarding the connection of mercury and AD, especially since there is an association between AD and serum mercury.

PESTICIDES AND HERBICIDES. Pesticides and herbicides have been implicated but the data is sparse and difficult to collect (105). In a study of a large cohort of Canadians, it was found that an increased risk of dementia was associated with residing in a rural area, as was occupational exposure to pesticides or fertilizers, which was suggested as the rural connection (106). Even the connection between trace pesticides or herbicides and cancer is controversial (107), but it is hard to argue against the wisdom of limiting exposure to any toxic chemical, just on general principles.

See Part I for References*

*published in July/August issue

INTERNATIONAL HEALTH NEWS is published 10 times a year by:
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E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com
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