

# **Aunt Cathy's Guide to Nutrition:**

**2008**

## **Nutrition Issues in Multiple Sclerosis**

("With References" Version)

**(For people with MS, their  
families and interested  
health care professionals)**

**MeritCare Health System**



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Multiple Sclerosis (MS) is an inflammatory disease of the myelin of the central nervous system, the origin of which is still unknown. Genetic, infectious, immunological and environmental factors have all been blamed, but none of these factors on their own can explain the whole spectrum of this disease.

### **There Are Two Major Areas of Concern Regarding Nutrition and MS:**

**Nutrition factors in the development and progression of MS**

**Nutrition problems resulting from MS and its treatment**

#### **Nutrients of interest in the development and progression of MS \***

\*(Each of these will be discussed in the following pages.)

- Vitamin D
- Fats (amounts and forms, such as saturated fat, monounsaturated fat, and omega-3 and omega-6 polyunsaturated fats)
- Antioxidants (e.g. vitamin E, selenium, alpha-lipoic acid, certain phytochemicals)
- B vitamins (B6, B12, folic acid, biotin)
- Minerals (magnesium, iron and phosphorus)
- Carnitine

#### **Nutrition issues will also interact with other factors:**

- Individual factors including genetic vulnerabilities, ethnicity, skin pigment and gender.
- Exposure to certain viral agents or other infectious agents during sensitive periods.
- Age at which a nutritional contributing factor to MS is experienced.
- Geographic variables such as latitude, altitude, soil mineral patterns and proximity to sea coasts.

**For ease of reading, only a few references will be included in the text.  
A large number of references will be grouped at the end of each section,  
and annotated references / abstracts will be included at the end of the paper.**

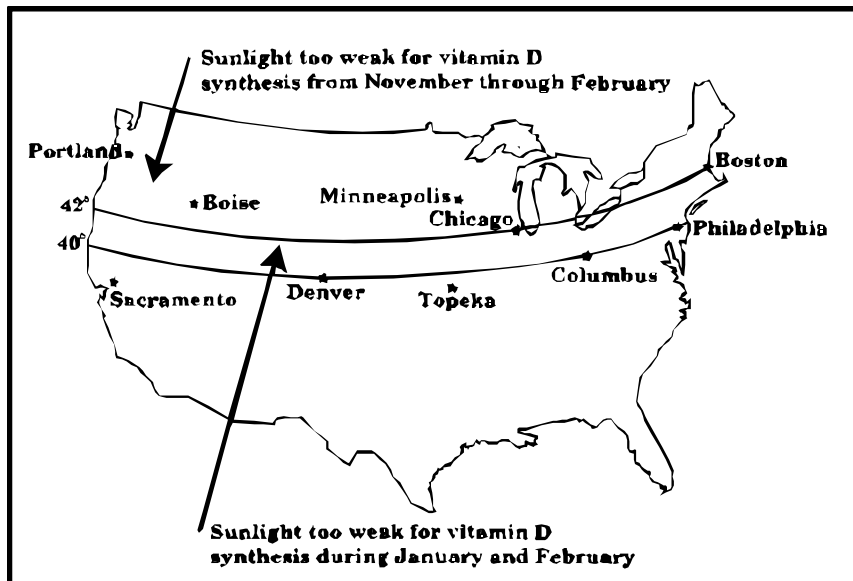
## Vitamin D

The results of large recent studies supported a protective effect of vitamin D intake on risk of developing MS. Some intervention trials have demonstrated that supplementation with vitamin D or its metabolites is able to improve symptoms of multiple sclerosis.

(Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006 Dec 20;296(23):2832-8. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest. 2005. Vitamin D intake and incidence of multiple sclerosis Neurology.,2004)

**Vitamin D inadequacy is related to the ability of the sun's rays to activate skin receptors. There is a clear latitude gradient, so that the likelihood of making inadequate vitamin D in the skin is greater in the north. Living in the north is also a known risk factor for MS, which is why the northern tier is called the "MS Belt" as well as the "Rickets Belt."**

The map below is from Tufts Health & Nutrition Newsletter 1996. It shows that sunlight is too weak for vitamin D synthesis from November through February at the 42<sup>nd</sup> parallel. Between the 40<sup>th</sup> and 42<sup>nd</sup>, the sunlight is too weak to make vitamin D in January and February. At that rate, it suggests that for every degree of latitude, there is an additional month of inadequate vitamin D production. The northern border is the 49<sup>th</sup> parallel across much of the USA. Alaskans and Canadians are even farther up there.



**Why have we assumed that people, especially those in the northern tier, are obtaining adequate vitamin D? I think we have missed this because we do not ordinarily obtain vitamin D levels as part of our regular health care assessment, and most**

importantly, because people with vitamin D deficiency do not look funny unless they are infants (who may develop the bowed legs of rickets, or other apparent bone deformity.) After childhood, the effects of vitamin D deficiency are often far less visible and unrecognized. Our nutrition health model has tended to be “If you don’t look funny, you must be fine.” Now that vitamin D levels are beginning to be done as part of health check-ups, it has been noted that there is actually “an unrecognized epidemic of vitamin D deficiency in the northern tier.” [The vitamin D epidemic and its health consequences. J Nutr. 2005 Nov;135(11):2739S-48S.]

**Fracture history and bone loss in patients with MS:** MS patients have significantly reduced bone mass and a high prevalence of abnormal vitamin D status. In one study, **in the absence of major trauma, fractures occurred in only 2% of controls but in 22% of MS patients.** After over two years of prospective follow-up both men and women with MS lost substantially more bone annually in the spine and in the femoral neck (the part of the leg bone where it meets the hip) than did the people without MS. Having had steroid treatment for more than 5 months, and a person’s ambulatory status (ability to walk) were both predictors of bone loss as well. (Vitamin D deficiency and reduced bone mineral density in multiple sclerosis: effect of ambulatory status and functional capacity. J Bone Miner Metab. 2005 Long-term effects of intravenous high dose methylprednisolone pulses on bone mineral density in patients with multiple sclerosis. Eur J Neurol. 2005 (Fracture history and bone loss in patients with MS. Neurology. 1998) Reduced bone mass and fat-free mass in women with multiple sclerosis: effects of ambulatory status and glucocorticoid use. Calcif Tissue Int. 1997)

**Nutrition Connection:** Bone loss in the spine occurred significantly faster in MS patients who had low 25-hydroxyvitamin D levels (<20 ng/mL). In those with normal levels, bone loss was insignificant. At the femoral neck, bone loss was substantial in all MS patients compared with controls, but was somewhat faster in the group with low vitamin D. These authors concluded that MS patients have more frequent fractures and lose bone mass more rapidly than do healthy age- and gender-matched peers, in part related to insufficient vitamin D. Vitamin D repletion might reduce the rate of bone loss and decrease osteoporosis-related fractures.

“**Vitamin D deficiency and reduced bone mineral density in multiple sclerosis: effect of ambulatory status and functional capacity.** J Bone Miner Metab. 2005;23(4):309-13 ...In conclusion, BMD is significantly lower in MS patients than in healthy controls, vitamin D deficiency is prevalent in MS, and ambulatory status is a determinative factor for osteoporosis in MS. Patients should be encouraged to have adequate sunlight exposure and to increase their mobility. Specific strengthening exercises for hip and back muscles in MS patients would have a substantial impact on bone density, osteoporosis, fracture risk, and mobility.”  
[CB comment: Since this was published it has become apparent that trying to solve the problem with sunlight exposure alone will be unsuccessful much of the year if you live up north. In other situations, the sunlight approach may be hampered by intolerance of warm weather. These and other reasons often make it necessary to approach the problem with supplemental vitamin D, either in milk or in vitamin pills. More on this later.]

**Genetic Defect in Vitamin D Metabolism?** 1,25-Dihydroxyvitamin D<sub>3</sub> is the hormone (biologically active) form of vitamin D. It exerts an immuno-suppressive effect and can completely prevent experimental autoimmune encephalomyelitis (EAE – the mouse model of MS.) Nataf et al (1996) and Cantorna et al (1996) reported that the non-activated vitamin D from diet or sunlight has no effect on mice with this condition. However, providing the 1,25 form of vitamin D resulted in decreased progression of EAE, and in some mice actual improvement of myelin injury. It is possible that failure to activate vitamin D may account for some forms of MS. Degrees of impaired activation may account for the variation seen in the severity of symptoms. And clearly, some people may have no genetic defect like this at all . . . they just have poor vitamin D intake and poor production in the skin (e.g. they live up north.)

The active (1,25-dihydroxy vitamin D exerts most of its actions only after it has bound to its specific receptors in the nucleus of a cell. Fukazawa et al. (1999) found an association of **MS with Vit D Receptor Gene (VDRG) polymorphism**. Polymorphism just means that the receptors on body cells that are looking for vitamin D apparently come in different forms in different groups of people. In other words, there appears to be variation in the form of the vitamin D receptor in some people. This may be another genetic trait involved in the development of MS. [Variation in the vitamin D receptor gene is associated with multiple sclerosis in an Australian population. J Neurogenet. 2005 Jan-Mar;19(1):25-38. ...Our results support a role for the VDR gene increasing the risk of developing multiple sclerosis, particularly the progressive clinical subtypes of MS. CTLA-4 gene polymorphism may modulate disease in Japanese multiple sclerosis patients. J Neurol Sci. 1999 Dec 1;171(1):49-55.]

### **Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety.**

Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations <140 nmol/L, which require a total vitamin D supply of 250 mcg (**10000 IU**)/d to attain. Published cases of vitamin D toxicity with hypercalcemia, for which the 25(OH)D concentration and vitamin D dose are known, all involve intake of > or = 1000 mcg (40000 IU)/d. Because vitamin D is potentially toxic, intake of >25 mcg (1000 IU)/d has been avoided even though the weight of evidence shows that the currently accepted “no observed adverse effect limit” of 50 mcg (2000 IU)/d is too low by at least 5-fold. (Risk assessment for vitamin D. Am J Clin Nutr. 2007 Jan;85(1):6-18. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. J Nutr. 2006 Apr;136(4):1117-22.)

**Point:** Since it now looks like 1000-2000 iu is needed up north just to assure adequate blood levels of vitamin D (which is important for many reasons,) and since this level is clearly safe, and since some people with MS are avoiding milk (the major dietary source of vitamin D,) **vitamin D supplementation is a very good idea**. It is not invasive or expensive. Assuring vitamin D adequacy may help to prevent the “excess” cases of MS seen in northern latitudes. Variations in diet or sun exposure that alter adequacy may explain some differences in severity and relapsing of symptoms. Some people may have a defect in activation of vitamin D to the active form, and may need to receive “calcitriol” (a prescription form of vitamin D that is already activated). **A one-time blood test** of 1,25 dihydroxy vitamin D level may be useful in identifying this problem if it exists. For more on vitamin D, please refer to one of my other handouts: **“Aunt Cathy’s Guide to Calcium and Vitamin D Supplements”**

**As can be seen below, the scientific research in this area is growing incredibly rapidly in just a short time.** I have put some shortened versions of the abstracts of some recent studies at the end of this paper for those of you who are interested in the actual studies, including the health care professionals who may be looking at this handout. (I want to be sure they believe me that I am not making this stuff up! ☺ )

However, the summary of it all is **“Yes . . . Vitamin D adequacy is a really big deal in MS.”** The vitamin D recommendations will be reviewed in the summary at the end of this paper. In the meantime, here is just a list of some vitamin D / MS References from 2000-2007.

## **2000- spring 2007 vitamin D and MS references**

### **2007**

Risk assessment for vitamin D. *Am J Clin Nutr.* 2007 Jan;85(1):6-18.

### **2006**

Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases.

*Anticancer Res.* 2006 Jul-Aug;26(4A):2581-8.

New insights into the mechanisms involved in the pleiotropic actions of 1,25-dihydroxyvitamin D<sub>3</sub>. *Ann N Y Acad Sci.* 2006;1068:194203.

Epidemiology and natural history of multiple sclerosis: new insights. *Curr Opin Neurol.* 2006 Jun;19(3):248-54

The role of vitamin D in multiple sclerosis. *Ann Pharmacother.* 2006 Jun;40(6):1158-61

Vitamin D & autoimmune disease--implications for practice from the MS literature. *J Am Diet Assoc.* 2006 Mar;106(3):418-24.

Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA.* 2006 Dec 20;296(23):2832-8.

Vitamin D and its role in immunology: MS, and inflammatory bowel disease. *Prog Biophys Mol Biol.* 2006 Sep;92(1):60-4

Vitamin D physiology. *Prog Biophys Mol Biol.* 2006 Sep;92(1):4-8.

1,25 Dihydroxyvitamin-D<sub>3</sub> modulates JAK-STAT pathway in IL-12/IFN $\gamma$  axis leading to Th1 response in experimental allergic encephalomyelitis. *J Neurosci Res.* 2006 May 15;83(7):1299-309.

Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog Biophys Mol Biol.* 2006 Sep;92(1):65-79.

The photobiology of vitamin D--a topic of renewed focus. *Tidsskr Nor Laegeforen.* 2006 Apr 6;126(8):1048-52.

IL-10 signaling is essential for 1,25-dihydroxyvitamin D<sub>3</sub>-mediated inhibition of experimental autoimmune encephalomyelitis. *J Immunol.* 2006 Nov 1;177(9):6030-7.

Vitamin D physiology. *Prog Biophys Mol Biol.* 2006 Sep;92(1):4-8.

Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr.* 2006 Apr;136(4):1117-22.

Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry.* 2006 Dec;14(12):1032-40.]

### **2005**

25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis. *Mult Scler.* 2005 Jun;11(3):266-71.

Why we should offer routine vitamin D supplementation in pregnancy & childhood to prevent MS. *Med Hypotheses.* 2005;64(3):608-18.

Effects of alfacalcidol therapy on serum cytokine levels in patients w multiple sclerosis. *Srp Arh Celok Lek.* 2005;133 Suppl 2:124-8.

A pilot study of oral calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) for relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2005 Sep;76(9):1294-6.

Vitamin D deficiency & reduced bone mineral density in MS: effect of ambulatory status & functional capacity. *J Bone Miner Metab.* 2005

Long-term effects of intravenous high dose methylprednisolone pulses on bone mineral density in patients with MS. *Eur J Neurol.* 2005.

Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest.* 2005.

The vitamin D epidemic and its health consequences. *J Nutr.* 2005 Nov;135(11): 2739S-48S.

Variation in the vitamin D receptor gene is associated with multiple sclerosis in an Australian population. *J Neurogenet.* 2005;19(1):25-38.

### **2004**

Why the optimal requirement for Vitamin D<sub>3</sub> is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol.* 2004 May;89-90(1-5):575-9.

Mounting evidence for vit. D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med* 2004;229(11):1136-42.

Multiple sclerosis and vitamin D: an update. *Eur J Clin Nutr.* 2004 Aug;58(8):1095-109.

Vitamin D intake and incidence of multiple sclerosis *Neurology.* 2004 Jan 13;62(1):60-5.

Dodging MS & RA with vitamin D. *Health News.* 2004;10 (3):4.

The pleiotropic actions of vitamin D. *Bioessays.* 2004;26(1):21-8.

D-vitamin: old paradoxes & new perspectives *Ugeskr Laeger.* 2004; 166(1-2):36-40.

### **2003**

The vitamin D deficit. *Science.* 2003 12;302(5652):1886-8.

Vitamin D target proteins: function & regulation. *J Cell Biochem.* 2003; 88(2):238-44.

Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr.* 2003.

### **2002**

Ultraviolet radiation & autoimmune disease: insights from epidemiological research. *Toxicology.* 2002;181-182:71-8.

Vitamins for chronic disease prevention in adults: clinical applications. *JAMA.* 2002; 287(23):3127-9.

### **2001**

Vitamin D: its role & uses in immunology. *FASEB J.* 2001;15(14): 2579-85

### **2000**

Vitamin D & autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence?. *Proc Soc Experi Biol Med.* 2000.

1,25-dihydroxyvitamin D<sub>3</sub> treatment decreases macrophage accumulation in the CNS of mice with experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2000.

Vitamin D: a natural inhibitor of multiple sclerosis. *Proc Nutr Soc.* 2000.

## **Total Fat Intake: The Swank Studies** (Swank & Dugan 1990.)

In this famous study, 144 MS patients followed a very low-fat diet for 34 years. Patients who adhered to the diet (which contained less than 20 g fat/day – a VERY small amount) showed significantly less deterioration and much lower death rates than did those who ate more fat. The greatest benefit was seen in those with minimum disability at the start of the trial. In this group, when those who died from non-MS diseases were excluded from the analysis, 95% survived and remained physically active. Only 20% who did not follow the diet survived for the whole the study period. **Interpretation Caution:** It has been argued that maybe those for whom the diet appeared to be helpful (that is, people doing well in terms of their MS) stayed on the diet, and those for whom it appeared to be unhelpful (those with worsening MS for whatever reason) gave up the diet and quit. So, maybe it was not the diet that accounted for the difference in outcome. Or maybe it was.

**Other observations:** Swank (1991) also found that women did better than men, and that patients treated early did better than when treatment was delayed. “High sensitivity to fats suggests that saturated animal fats are directly involved in the genesis of multiple sclerosis.” In addition to the issue of Total Amount of Fat in the diet, the Forms of Fat may be an important factor. The distinctions between the various forms of dietary fats being investigated now in this area had not been identified at the time the Swank studies were undertaken.

**Biological effects of fish oils in relation to chronic diseases.** Omega-3 marine lipids (polyunsaturated fish oils) affect the types of substances called eicosanoids produced in the body. These include important substances like prostaglandins, leukotrienes, prostacyclins, and thromboxanes. The involvement of prostaglandins and leukotrienes in immune responses has led to studies on the effects of fish oil on various chronic diseases associated with abnormalities of the immune system, such as MS. One example of an early observation was that Greenland Eskimos have a high intake of seal, whale and fish, (rich sources of Omega-3 marine lipids), and MS is uncommon in Eskimos.

**Supplementation of Polyunsaturated Fatty Acids (PUFAs).** In 1990, Bates reviewed published controlled trials of omega-6 PUFAs involving 172 patients with acute remitting MS and one study with omega-3 PUFAs in a double blind controlled study of 312 patients. A trend was found suggesting that the addition of omega-6 and omega-3 PUFAs to the diet of patients with MS results in a reduction of the severity and frequency of relapses and in a mild overall benefit in a two year period.

**Omega-3 polyunsaturated fatty acids and cytokine production in health and disease.** In 1997, Calder studied eicosanoids made from omega-6 oils because they modulate the production of pro-inflammatory and immunoregulatory substances called cytokines. Overproduction of these cytokines is associated with both septic shock and chronic inflammatory diseases. **The omega-3 polyunsaturated fatty acids (PUFAs) called EPA and DHA are found in fish oils.** They suppress the production of the eicosanoids made from Omega-6 PUFAs. EPA is used for making an alternative family of eicosanoids that are less inflammatory. So, dietary fats which are rich in omega-3 PUFAs have the

potential to alter cytokine production (Gallai et al. 1995 Endres & von Schacky 1996.) Deficiencies of PUFAs and replacement by nonessential forms of fat has been reported in the plasma lipids in multiple sclerosis (Holman et al. 1989.) They found that phospholipids in people with MS have normal levels of (omega 6) linoleic acid and the next fatty acid in the pathway to make eicosanoids was elevated. But all the omega 6 fatty acids greater than 18 carbons long were subnormal in MS. This pattern is an indication of impaired ability to add carbons to lengthen the carbon chain to make the eicosanoids. **All the omega-3 acids were found to be subnormal in people with MS.**

**Depression in MS** Hibbeln and Salem (1995) reported that decreased omega-3 fatty acid intake (especially DHA) correlates with increasing rates of depression, and this may be a factor in depression in MS. Depressed individuals with MS have a worse outcome than non-depressed individuals. There is now evidence of impaired phospholipid metabolism and impaired fatty acid-related cell communication processes. Impaired phospholipid and fatty acid metabolism (e.g. involving DHA – an omega-3 fat that is critical for brain function) may be a primary cause of depression in many patients and may explain the interactions with MS and other diseases (Horrobin & Bennett, 1999.) Additionally, there are depression issues related to (what else?) Vitamin D and folic acid (a B vitamin discussed later.) Specific MS-related research with omega-3 fats and other polyunsaturated fats is limited, although the research on benefits of these fats in many aspects of human health is quite impressive. More information about wider applications is available in my handouts on line on various types of fats and oils. [Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry. 2006 Dec;14(12):1032-40.]

Here are some of the most recent reports investigating the role of various forms of fat specifically in MS:

**Polyunsaturated fatty acids and neurological diseases.** Mini Rev Med Chem. 2006 Nov;6(11):1201-11. This review summarizes the knowledge of the role of dietary PUFAs, especially omega-3, on normal brain function. It reports the evidence pointing to potential mechanisms of omega-3 fatty acids in development of neurological disorders and efficacy of their supplementation in terms of symptom management.

**Antioxidants and polyunsaturated fatty acids in multiple sclerosis.** Eur J Clin Nutr. 2005 Dec;59(12):1347-61. These authors concluded that “Both dietary antioxidants and PUFAs have the potential to diminish disease symptoms by targeting specific pathomechanisms and supporting recovery in MS.”

**Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients.** Prostaglandins Leukot Essent Fatty Acids. 2005 Nov;73(5):397-404. This study suggests that “a low fat diet supplemented with omega-3 PUFA can have moderate benefits in RRMS patients on concurrent disease modifying therapies.”

**Polyunsaturated fatty acid supplementation in MS.** Int MS J. 2005 Nov;12(3):88-93. This article focuses on polyunsaturated fatty acid (PUFA) supplementation. Small-scale studies have demonstrated trends towards some beneficial effects. PUFA supplementation is generally well tolerated, although some specific supplements are best avoided and some clinical situations warrant caution. A review of the efficacy and safety data suggests that PUFA supplementation may be a promising approach. Large-scale trials are required to confirm the benefits.

**Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases.** Evid Rep Technol Assess (Summ). 2005 Feb;(114):1-3.

**Omega-3 fatty acids in health and disease: part 2--health effects of omega-3 fatty acids in autoimmune diseases, mental health, and gene expression.** J Med Food. 2005 Summer;8(2):133-48.

**Omega-3 fatty acids in inflammation and autoimmune diseases.** J Am Coll Nutr. 2002 Dec;21(6):495-505. “... There have been a number of clinical trials assessing the benefits of dietary supplementation with fish oils in several inflammatory and autoimmune diseases in humans, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis and migraine headaches. Many of the placebo-controlled trials of fish oil in chronic inflammatory diseases reveal significant benefit, including decreased disease activity and a lowered use of anti-inflammatory drugs.”

## **Antioxidants.**

Reactive Oxygen Species (ROS) are byproducts of metabolism that are thought to be involved in causing or contributing to MS and also to experimental allergic encephalomyelitis (EAE – the mouse model of MS.) Another common name for ROS is “**free radical.**” These substances can cause injury to a person’s cells if they are not handled properly (that is “quenched” or “extinguished” by substances called antioxidants.)

Van der Goes et al. (1998) found that phagocytosis of myelin by macrophages triggers the production of ROS. Free radical action has been suggested as a causal factor in multiple sclerosis (J Neurol 1999.) For example: malondialdehyde in the blood (a marker for low vitamin E or other antioxidant protection) was increased by 38% during MS exacerbations (periods of worsening symptoms.) These changes suggest that there is increased free radical (ROS) production and consumption of the scavenger molecules during the active phase of the disease.

**Demyelination: the role of reactive oxygen and nitrogen species.** Smith et al.(1999) found that reactive oxygen (ROS) and nitrogen species (RNS) play a role in demyelination, such as in the inflammatory demyelinating disorders like multiple sclerosis. The concentrations of reactive oxygen and nitrogen species (e.g. superoxide, nitric oxide & peroxynitrite) can increase dramatically under conditions such as inflammation. This can overwhelm the person’s antioxidant defenses within tissues.

Such oxidative and/or nitrative stress can damage the lipids, proteins and nucleic acids of cells and mitochondria, potentially causing cell death. **The reactive species (ROS and RNS) may also damage the myelin sheath, promoting its attack by macrophages.** Damage can occur directly by lipid peroxidation, and indirectly by the activation of proteases and phospholipase A2. The neurological deficit resulting from experimental autoimmune demyelinating disease has generally been reduced by trial therapies [that is, antioxidants] that diminish the concentration of reactive oxygen species. However, therapies aimed at diminishing reactive nitrogen species have had a more variable outcome, sometimes exacerbating disease.

**Selenium Issues:** Selenium (Se) is a mineral in the news in many areas of medical research, such as diabetes, prostate cancer, thyroid disease, immune system function and multiple sclerosis (Foster HD,1993.) Glutathione peroxidase is a very important antioxidant in the body and selenium is a key component of it. Mazzella et al., (1983) found that the **Se-dependent glutathione peroxidase activity in the red blood cells was lower in the MS patients.**

In addition, **the Se concentration in the diet of MS patients was studied and found to be less than the minimum values suggested by the US Food and Nutrition Board.**

The authors’ interpretation: “Modified glutathione peroxidase activity found in erythrocytes [red blood cells] of MS patients is independent from the Se concentration in blood.” The reported dietary inadequacy was not addressed further.

**My observations:** It is likely that suboptimal Se intake affects various tissues differently, and that possibly the blood levels had a “higher priority” for the Se available. In view of

new knowledge about the significant health risks associated with Se inadequacy, it is a good idea to assure an intake within recommended ranges (60-150 mcg). Studies in the late '90s have revealed that dietary Se intakes are sub-optimal in diets of many people. This is especially true in certain geographic regions (such as Phoenix, AZ) where the soil is quite low in selenium.

It is very hard to estimate a person's actual selenium intake because it is so variable in foods. Selenium is an unusual mineral because the amount in a food depends on where it was produced, and especially in this country, that can be difficult to determine. Excessive selenium intake can be toxic however, so the upper limit of safety is set at 600 mcg/day, and the level regarded as toxic is a regular intake of 800 mcg/day. My handouts on "Nutrition and Eye Health" and "Nutrition in Prostate Cancer" both contain additional information, as selenium and the selenium-containing antioxidant glutathione peroxidase are looking very important in general. It is also being found to be very important in the operation of the immune system and the thyroid gland.

**Other potent antioxidants are also being explored in relation to MS, such as "alpha-lipoic acid."** This substance is also looking to be potentially very beneficial in diabetes, most specifically with some of the neurologic problems (neuropathy) experienced by people with diabetes over time. In general, it appears that any inflammatory or autoimmune condition results in greater production of free radicals, and so as a generality, a more generous intake of antioxidants is reasonable.

Alpha-lipoic acid is similar to B vitamins in several ways. It is extremely unlikely to be toxic even at high doses. Most studies have shown that about 600 mg/day over time is the level associated with measurable benefits in diabetes research.

**It is also reasonable (and a very good idea) to seek out generous potent dietary antioxidants (like the brightly colored pigments fruits and vegetables . . . lycopene, anthocyanins, lutein, etc.)** The antioxidant vitamins (C and E) are not nearly as potent as antioxidants as the plant pigments are. For example, lycopene (the red color in tomatoes) is 200 times as potent an antioxidant as vitamin E. These substances are not vitamins or minerals, but they fall into a class called "phytochemicals" which just means "plant chemicals."

Not all plant chemicals in the world are safe, of course . . . consider poison ivy and opium, for example. However, the family of these plant pigments (called carotenoids) are very safe. The only side effect is that eating lots of beta-carotene in carrots, squash and sweet potatoes may give your skin a harmless orange-ish glow. [That can pass for a tan up here in North Dakota! ☺] The huge health benefits now being recognized is the reason behind the recent change from the familiar "Five-a-Day" recommendation for fruits and vegetables in everyone's diet to something approximating:

**“Eat a whole bunch of brightly colored vegetables and fruits every day for a whole bunch of reasons!!!!”**

## **Antioxidants and MS:**

**Here is a list of the most recent research specifically about antioxidants and MS. An annotated set of references / abstracts follows at the end of this paper for people who want more detail.**

### **2006**

Dietary chelators as antioxidant enzyme mimetics: implications for dietary intervention in neurodegenerative diseases. *Behav Pharmacol.* 2006 Sep;17(5-6):425-30.

Antioxidants in multiple sclerosis: do they have a role in therapy? *CNS Drugs.* 2006;20(6):433-41.

Dual effects of antioxidants in neurodegeneration: direct neuroprotection against oxidative stress and indirect protection via suppression of glia-mediated inflammation. *Curr Pharm Des.* 2006;12(27):3521-33.

### **2005**

Antioxidants and polyunsaturated fatty acids in multiple sclerosis. *Eur J Clin Nutr.* 2005 Dec;59(12):1347-61.

Lipoic acid in multiple sclerosis: a pilot study. *Mult Scler.* 2005 Feb;11(1):24-32.

The role of metallothioneins in experimental autoimmune encephalomyelitis and multiple sclerosis. *Ann N Y Acad Sci.* 2005 Jun;1051:88-96

Time-course expression of CNS inflammatory, neurodegenerative tissue repair markers and metallothioneins during experimental autoimmune encephalomyelitis. *Neuroscience.* 2005;132(4):1135-49.

### **2004**

Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis. *J Immunol.* 2004 Nov 1;173(9):5794-800.

Alpha lipoic acid inhibits human T-cell migration: implications for multiple sclerosis. *J Neurosci Res.* 2004 Nov 1;78(3):362-70.

Protective effects of caffeic acid phenethyl ester against experimental allergic encephalo-myelitis-induced oxidative stress in rats. *Free Radic Biol Med.* 2004 Aug 1;37(3):386-94

The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *J Neurol.* 2004 Mar;251(3):261-8.

Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2004 Mar;148(1-2):146-53.

### **2003**

Bilirubin as a potent antioxidant suppresses experimental autoimmune encephalomyelitis: implications for the role of oxidative stress in the development of multiple sclerosis. *J Neuroimmunol.* 2003 Jun;139(1-2):27-35.

### **2002**

Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2002 Oct;131(1-2):104-14.

## **My comments on all these fat and antioxidant issues:**

Different types of fat and the adequacy of antioxidant protection interact with each other. Clearly there is deranged metabolism of fatty acids in MS. Is it a cause of MS, or the result of having MS? Can it be manipulated? Future directions of research should include evaluating these substances together and not just as individual agents. For example, it would be useful to study:

- Comparisons of ratios of omega 3 to omega 6 PUFAs (PolyUnsaturated Fatty Acids), with attention also paid to the ratios of antioxidants to PUFAs.
- Evaluation of fat issues while accounting for oxidation status.
- Fish x Fat x Antioxidants Antioxidants inhibit the enzyme lipoxygenase and so inhibits leukotriene synthesis. The fish oil leads to production of less inflammatory leukotrienes. Antioxidants also protect the fish oils from oxidation We need to learn which of these factors can be useful in trying to prevent the development of MS, or slow its progress.
- Differentiate in the study between omega-3 and omega-6 PUFAs in terms of the size of the molecule (shorter vs longer chain length,) because this is now looking like an important feature to consider in research related to many other health conditions.

Issues involving dietary fat and antioxidants are intimately related. For more detail on these issues, including food sources and supplement considerations, please see my other handouts “**Aunt Cathy’s Guide to Eye Health**” (for more information about antioxidants) and “**Aunt Cathy’s Guide to Omega 3 Fatty Acids.**”

## **Other areas of investigation-- B Vitamins:**

### **Biotin, Vitamin B6, Vitamin B12, and Folic Acid**

**What the Heck is Biotin?** It is a B vitamin involved in many body functions that process carbohydrates, fats and proteins. The recommended intake is 30-100 mcg (based on reported dietary intakes in healthy people in the US.) Biotin is not toxic, even at levels as high as 10,000 mcg/day (1000 times the upper end of the assumed adequacy level.)

**Bacteria in the intestine produce biotin and they contribute a significant amount, so getting an adequate amount is unlikely for any person who chronically uses antibiotics, unless biotin is supplemented.** Symptoms of inadequacy include “tingling in extremities.”

Biotin is a B vitamin that usually receives little attention, since most people obtain an adequate amount from the intestinal bacteria. However, it is looking interesting in other autoimmune diseases such as diabetes. (The effect of chromium picolinate and biotin supplementation on glycemic control in poorly controlled patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized trial. *Diabetes Technol Ther.* 2006 Dec;8(6):636-43. Use of chromium picolinate and biotin in the management of type 2 diabetes: an economic analysis. *Dis Manag.* 2005 Aug;8(4):265-75.)

There is little activity in the MS research at present. However, Anagnostouli et al.(1999), looked at concentrations in human cerebral-spinal fluid (CSF) & blood serum. Patients with common neurologic disorders (including MS) were compared with people who had no evidence of nutritional or neurologic disorders. They found significantly lower values for biotin in people with MS (both CSF & serum). They concluded that this low level could be the result of poor biotin absorption in the intestine caused by the underlying disease, or related to a biotin-binding immunoglobulin which may be involved in MS development and progression.

**Vitamin B6 (Pyridoxine)** It is well known that this vitamin plays a vital role in many physiological processes, such as nerve communication, processing protein and fats, and supporting the immune system. Levels higher than the RDA appear to have be of some benefit in decreasing damage to nerves in other autoimmune conditions such as diabetes. In many of these activities, vitamin B6 is paired with the mineral magnesium (more on magnesium later) and it appears that both substances need to be present at the same time for efficient operation. This is just one more situation in which studying a single nutrient is unlikely to be as useful as studying them in combination.

Of all the B vitamins, B6 is the most likely to be a problem in very high doses for a pretty long time . . . such as 200-500 mg/day chronically in the most sensitive individuals. (The RDA level is only 1-2 mg.) Interestingly, the symptoms associated with the highest doses, while rare, include some MS-like tingling in the arms. The idea that an

unrecognized inadequacy of vitamin B6 might be a factor in MS comes from just one study: “Serious dangers to health may be associated with undetected, lingering subclinical deficiencies . . . This includes induction of and predisposition to diseases such as atherosclerosis and multiple sclerosis” (Kesel et al. 1999.)

**Vitamin B12:** Vitamin B12 levels have been low in MS patients in many studies. The significance of this is unclear. Is it related to poor absorption? Is it poorly utilized or kept in the wrong compartments in the body? (Goodkin, 1994) Low vitamin B12 status may increase vulnerability to the viral and immunologic processes which are suspected as being factors in causing MS. **Certainly, adequacy of vitamin B-12 has critical importance to neurologic health (for everyone).**

**Some individuals are at special risk of poor vitamin B12 status. Some patients may be following strict vegetarian diets with inadequate vitamin B12, or using medications such as Glucophage (also called Metformin) for diabetes. Others take medications that block production of stomach acid called “proton pump inhibitors,” such as Prilosec, Prevacid, Protonix, Pepcid AC, and Nexium.**

Any of these situations will increase the likelihood of impaired vitamin B-12 availability and/or absorption. Additionally, as we age, some people simply begin to produce much less acid in their stomachs. **Inadequate stomach acid decreases our ability to absorb vitamin B12 from food sources. However, the form found in vitamin pills and fortified cereals is far more reliably absorbed in spite of these problems.**

**Because of this, 15-30% of the elderly are found to be deficient in this critical vitamin when their level is actually checked with a sensitive measure.** (Waiting and watching for changes to appear in red blood cell size is not a sensitive measure because it is a very late-appearing symptom of vitamin B12 deficiency.) Assuring a generous intake of absorbable vitamin B-12 is not difficult or expensive. For most people simply taking a multivitamin supplement prevents this problem. In some studies described below, vitamin B12 administered with other therapeutic agents may have some benefit in MS, although a straightforward vitamin B12 deficiency is apparently not the reason. For more information about vitamin B-12 issues, please see my other hand-out “**Aunt Cathy’s Guide to Vitamin B-12.**”

**Here are some recent research regarding Vitamin B12 and MS. An annotated / abstract reference list follows at the end of this paper.**

**2006**

Vitamin B12, folic acid, and the nervous system. *Lancet Neurol.* 2006 Nov;5(11):949-60.

Vitamin B12 and methionine synthesis: a critical review. Is nature’s most beautiful cofactor misunderstood? *Biofactors.* 2006;26(1):45-57.

Plasma homocysteine levels in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2006 Feb;77(2):189-92.

**2005**

Vitamin B12, demyelination, remyelination and repair in multiple sclerosis *J Neurol Sci.* 2005 Jun 15;233(1-2):93-7.

**2004**

Attenuation of experimental autoimmune encephalomyelitis and nonimmune demyelination by IFN-beta plus vitamin B12: treatment to modify notch-1/sonic hedgehog balance. *J Immunol.* 2004 May 15;172(10):6418-26.

**2003**

Increased plasma homocysteine levels without signs of vitamin B12 deficiency in patients with multiple sclerosis assessed by blood and cerebrospinal fluid homocysteine and methylmalonic acid. *Mult Scler.* 2003 Jun;9(3):239-45.

Lipoprotein oxidation, plasma total antioxidant capacity and homocysteine level in patients with multiple sclerosis. Nutr Neurosci. 2003 Jun;6(3):189-96.

**2002**

Treatment of multiple sclerosis with lofepramine, L-phenylalanine and vitamin B(12): mechanism of action and clinical importance: roles of the locus coeruleus and central noradrenergic systems. Med Hypotheses. 2002 Nov;59(5):594-602.

A randomised placebo controlled exploratory study of vitamin B-12, lofepramine, and L-phenylalanine (the "Cari Loder regime") in the treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2002 Sep;73(3):246-9

**Other B-vitamins and Iron:** Regeneration of myelin requires both adequacy of iron and of B vitamins, especially vitamin B12 and folic acid. This situation is a good illustration of the problems inherent in evaluating the effects of manipulating or measuring a single nutrient to detect benefit. Many if not most important nutrient-related effects require the adequacy of several nutrients working together and so the common type of "single-nutrient research" will often fail to detect and identify important roles of that nutrient.

**Iron and the folate-vitamin B12-methylation pathway in multiple sclerosis.** Metab Brain Dis. 2006 Sep;21(2-3):121-37. Some subjects with multiple sclerosis (MS) present with low blood iron parameters. Anecdotal reports and a single patient study suggest that iron supplementation may be beneficial in these subjects. **Myelin is regenerated continually, but prerequisites for this process are iron and a functional folate-vitamin B12-methylation pathway.** The aim of this study was to determine iron status, folate and homocysteine in MS subjects, and to evaluate the effect on MS symptoms if deficiencies were addressed. **Results: In relapsing-remitting MS subjects, serum iron concentration correlated significantly with age at diagnosis (r=0.49; p=0.008). In Caucasian female MS subjects, serum iron and ferritin concentrations were significantly lower than in matched controls. In a 6-month pilot study, 12 subjects taking a regimen of nutritional supplements designed to promote myelin regeneration, improved significantly neurologically as measured by the Kurzke EDSS (Total Score means 3.50 to 2.45, 29.9%; p=0.021). These were significantly improved (p=0.002) compared to 6 control group patients taking multivitamins (Kurzke Score increased by 13.9% from 4.83 to 5.50). Both groups had significantly reduced homocysteine concentrations at 6 months, suggesting that methylation is necessary but not sufficient for myelin regeneration.**

**Magnesium:** Magnesium (Mg) is involved in the **activity of over 300 enzymes** in the body, and it is **very critical in neurologic health**. As mentioned earlier, magnesium and vitamin B6 very often work together in this role. Stelmasiak et al. (1995), found a **significant decrease of Mg concentration in red blood cells and no changes in blood plasma of MS patients compared with controls**. This suggests the presence of changes in red blood cells which could be connected with their shorter life and impaired function in MS. Magnesium is known to be decreased in central nervous system (CNS) tissues of people with MS. Yasui & Ota (1992) note that with Mg depletion, pathologic changes are seen especially in white matter, and this may contribute to the development of MS.

**Magnesium Adequacy:** Inadequate Mg intake is common in the general population. In fact, a large national survey\* of Americans done every ten years by the Center for Disease Control (the CDC) found that **the majority of Americans obtain less than 2/3 of the Recommended Dietary Allowance for this nutrient**. Certainly there is every reason to assure that the common dietary inadequacy of magnesium does not complicate problems for individuals with MS, since magnesium has so many important roles in neurologic function. (\*NHANES – National Health And Nutrition Examination Survey.)

There is little MS-specific magnesium research being reported, but I found three items to include here:

**Importance of magnesium depletion with hypofunction of the biological clock in the pathophysiology of headaches with photophobia, sudden infant death and some clinical forms of multiple sclerosis.** Magnes Res. 2004 Dec;17(4):314-26. ... MS may be associated with primary disorders of BC Clinical forms of Mg depletion with hBC in MS present diurnal exacerbations and relapses during fair seasons....

**The multifaceted and widespread pathology of magnesium deficiency.** Med Hypotheses. 2001 Feb;56(2):163-70. ...The very small probability that all the variables affecting Mg levels will behave favorably, results in a high probability of a gradually intensifying Mg deficiency. It is highly regrettable that the deficiency of such an inexpensive, low-toxicity nutrient result in diseases that cause incalculable suffering and expense throughout the world. The range of pathologies associated with Mg deficiency is staggering: hypertension (cardiovascular disease, kidney and liver damage, etc.), peroxynitrite damage (migraine, **multiple sclerosis**, glaucoma, Alzheimer's disease, etc.)

**The effect of magnesium oral therapy on spasticity in a patient with multiple sclerosis.** Eur J Neurol. 2000 Nov;7(6):741-4. The effects of magnesium glycerophosphate oral therapy on spasticity was studied in a 35-year-old woman with severe spastic paraplegia resulting from multiple sclerosis (MS). We found a **significant improvement in the spasticity after only 1 week from the onset of the treatment** on the modified Ashworth scale, an improvement in the range of motion and in the measures of angles at resting position in lower limbs. No side-effects were reported and there was no weakness in the arms during the treatment.

In view of the many roles of Mg (especially in the central nervous system) and the true likelihood that one's diet may in fact provide too little magnesium, it is reasonable to take steps to assure that Mg intake at least meets RDA levels. **Magnesium Food Sources:** Best are nuts, peanuts and other legumes, whole grains, wheat germ and bran. If a person avoids these foods (e.g. out of concern about the fat content or the calories in nuts or peanut butter,) realize that a supplement is likely necessary to prevent inadequacy. Most general multivitamins have only 0-25% of the RDA, so read the label. For more information about magnesium, please see my other handout **"Aunt Cathy's Guide to Magnesium."**

### **One study suggested that phosphate adequacy may be a factor in MS:**

**Phosphate depletion is the link between growth, stress and diet in the aetiology of MS.** Med Hypotheses. 2004;63(2):262-7. . . . Phosphate depletion results in demyelination. Phosphate depletion (PD) can lead to neurological complications, which have been characterized in experimental & clinical studies. Hypophosphataemia, whether acute or chronic, induced by stress from accident, surgery or burns, by infection and/or undernutrition, is therefore an important etiological factor. Low SP levels have been reported in MS patients & the hypothesis that PD causes MS is presented here.

## **Carnitine**

Carnitine is a substance made by the body and also found in meats. It is important inside cells for converting fat into energy. There is currently a lot of interest in carnitine in a wide variety of medical applications. In MS, the applications have been aimed at helping with fatigue, as reported in these studies:

**Levocarnitine administration in multiple sclerosis patients with immunosuppressive therapy-induced fatigue.** Mult Scler. 2006 Jun;12(3):321-4. Nutritional factors and comedications are among the postulated causes of fatigue, a highly prevalent symptom in the multiple sclerosis (MS) population, with serious impact on patients' quality of life. Deficiency of carnitine may play a role by reducing energy production through fatty acid oxidation and numerous MS therapies can induce fatigue syndrome. The aim of this prospective open-labelled study was to collect and study serum carnitine levels in MS patients with and without disease-modifying treatment-induced fatigue syndrome. We investigated whether restoration of the carnitine pool might improve treatment-induced fatigue in MS

patients. In our study, there was no statistical difference in fatigue frequency between treated and untreated patients (P=0.5). Matched to age, gender and treatments, carnitine levels were lower for MS treated patients compared to untreated MS patients (P <0.05) or controls (P <0.001). Consecutive patients with low plasma carnitine levels who experienced fatigue were substituted. Treatment consisted of oral levocarnitine, 3-6 g daily. All patients achieved normal plasma carnitine levels. **For 63% of patients treated with immunosuppressive or immunomodulatory therapies, oral levocarnitine adjunction decreased fatigue intensity, especially in patients treated with cyclophosphamide and interferon beta.**

**Treatment of multiple sclerosis-related fatigue: pharmacological and non-pharmacological approaches.** *Neurol Sci.* 2006 Sep;27(Supplement 4):s297-s299. Fatigue is a common symptom in multiple sclerosis (MS). As fatigue includes a variety of aspects, its treatment is best approached in a multidisciplinary fashion that includes nonpharmacological interventions and medications. In individuals with mild fatigue non-pharmacological treatment including yoga, aerobic exercises, cooling therapy and energy conservation techniques might be considered. Several pharmacological treatments for patients with significant fatigue have proved to be effective. Among these agents, amantadine and aminopyridines are the most frequently used. **More recently also aspirin and carnitine have been used to treat MS fatigue but they need to be confirmed in larger studies.**

**Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial.** *J Neurol Sci.* 2004 Mar 15;218(1-2):103-8. Treatment with acetyl L-carnitine (ALCAR) has been shown to improve fatigue in patients with chronic fatigue syndrome, but there have been no trials on the effect of ALCAR for treating fatigue in multiple sclerosis (MS)...Statistical analysis showed significant effects of ALCAR compared with amantadine for the Fatigue Severity Scale (p = 0.039). ... **The results of this study show that ALCAR is better tolerated and more effective than amantadine for the treatment of MS-related fatigue.**

## **Nutrition problems due to MS and its treatment**

- avoidance of “suspect” foods
- dysphagia
- weight / body composition
- pressure ulcers (also called “bed sores”)
- bladder infection
- drug/nutrient interactions

### **Avoidance of “suspect” foods.**

Many people try a variety of dietary changes in the hope that it will help control the symptoms of MS. It is especially important in this situation that a knowledgeable person review the total intake picture to assure that important nutrients are not accidentally obtained in inadequate or excessive amounts.

**Oral flavonoids delay recovery from experimental autoimmune encephalomyelitis in SJL mice.** ...Our results indicate that oral flavonoids fail to beneficially influence the course of EAE in mice but, instead, suppress recovery from acute inflammatory damage. *Biochem Pharmacol.* 2005 Jul 15;70(2):220-8.

**Exacerbation of protracted-relapsing experimental allergic encephalomyelitis in DA rats by gluten-free diet.** ... Here we study the effects of a gluten-free diet on the course of protracted-relapsing EAE in DA rats, serving as a preclinical model of human MS. The data show not only that this nutritional approach failed to ameliorate development of the disease but rather that it exacerbated the course. *APMIS.* 2004 Oct;112(10):651-5

### **Dysphagia**

Abnormal swallowing is common in MS although people often do not complained of it. It is associated with disordered brainstem/cerebellar function, overall disability, depressed mood and low vital capacity (Thomas & Wiles, 1999.) Assure that any textural manipulations to facilitate safe eating (such as thickening beverages) do not disrupt nutritional adequacy. For example, some people actually get a third of their calories just from the starchy thickeners. **This will either result in excessive weight gain if they continue to eat the**

**same amount of food, or it will contribute to poor nutrient intake if the total food intake is cut back to avoid weight gain.**

The best foods are those which have generous amounts of vitamins, minerals and beneficial phytochemicals relative to the number of calories they provide. These desirable foods are said to be “**nutrient dense.**” Starchy thickeners are not nutrient dense at all, and if a person must use them for safety of swallowing, appropriate nutrient supplementation will be even more important than usual. A few commercial thickening products are available that do contribute some vitamins and minerals, but most do not. If assuring adequate food/nutrient intake orally becomes a problem, it has been shown that a **percutaneous gastrostomy tube** can be very useful and improve quality of life significantly. (Acta Gastroenterol Latinoam 2004)

### **Weight / Body Composition:**

Many evaluations of nutritional status only look at Body Mass Index (BMI) or some other weight-related measure. It is important to consider the alterations in body composition that occur with increasing immobility. As mobility decreases, a person’s “Lean Body Mass” will also decrease, resulting in a lower requirement for total calories. Failure to adjust calories downward can contribute to overweight and increased mobility for people with MS. However, as described above, when caloric requirements and total intake decrease, there is an increased risk of missing out on essential nutrients.

**Supplementation is reasonable, and it will be necessary in almost all instances.**

### **Pressure Ulcers:**

Weight influences on mobility can affect risk of pressure ulcers. However, although optimal protein and micronutrient nutrition is critical in preventing or healing pressure ulcers, they are often poorly provided when the calorie intake is low. Immobilization contributes to both the “pressure” and to the likelihood of inadequate intake of micronutrients. **Again, supplementation will be necessary in almost all instances.**

### **Bladder Infection:**

Cranberry juice may be helpful, not because of acidification of urine, but because of the effects of a natural substance in cranberries that helps make bacteria less likely to adhere to the bladder lining. **A generous intake of fluids is also helpful. However, remember to watch the calories provided by beverages.** For example, “cranberry juice cocktail” has a lot of sugar added because it is otherwise too tart. The result is a beverage with 20 calories per oz -- the same calories as whole milk! Using artificially sweetened cranberry juice provides the benefits of cranberry in a very small amount of calories.

**Drug/Nutrition Interactions:** Chronic use of antibiotics is known to impair folic acid absorption, and it also stops biotin and vitamin K production by intestinal bacteria. Several specific interactions were described in the section of vitamin B-12 earlier, and there are many other interactions of potential importance. Some medications can also affect appetite, swallowing, mouth dryness, and elimination patterns which indirectly influence the likelihood of obtaining appropriate nutrition. **It is always important to evaluate the potential for drug/nutrient interactions, so ask your physician,**

**pharmacist or dietitian if there are any important issues with the particular medications you are taking.**

**Reproductive Health Note:**

**Infant health of mothers with multiple sclerosis.** West J Nurs Res. 2004 Oct;26(6):632-49. “Controversy surrounds whether mothers with multiple sclerosis (MS) who wish to breast-feed their infants should forego breast-feeding in order to resume immunomodulating therapy following birth even though breast-feeding has not been shown to have deleterious effects on these mothers. . . . Significantly more non-breast-fed than breast-fed infants experienced otitis media, lower respiratory illness, constipation, milk intolerance, & allergy during the 1st year. Study results support the need to encourage mothers with MS who wish to breast-feed their infants to do so and to delay immunomodulating therapy until breast-feeding cessation.”

**IN SUMMARY:**

**My Best Guess (subject to change at any moment based on new research) about diet/nutrients to decrease risk of MS and/or decrease the rate of progression:**

**First: Try not to be Scottish, Irish, female, or to have lived up here in North Dakota when you were 15. Select your parents and other family members very carefully.** [I realize, of course, that we have no control over these particular factors. However, recognizing these factors as important may help individuals to evaluate or even take steps to modify their own personal risk or the risk to others in the family.]

**Second: Look Closely to Assure Adequacy of All Nutrients.** This is true for everyone, of course. The diet should be “nutrient dense” (lots of nutrients per calorie, or per volume) because total food intake is often low. Realize that some people with MS are avoiding fat, milk and meat, so vitamin D, vitamin B6, calcium, zinc, iron and protein intake are all likely to be suspect.

**Third: Specific Food and Nutrient Risk Issues**

Realize that **to achieve adequacy of Vitamin D requires 1000-2000 iu for many people up north** – more than the usual RDA level-- and that **inadequacy may be a factor in the development and/or progression of MS.** Any people who are covered up, who have dark skin, who have old skin, who use sunscreen, or who often stay indoors should certainly aim for this amount of vitamin D from food and/or supplements. Interestingly, the same goes for people who have none of these risks . . . it may be protective against a number of serious health problems, and that amount is clearly safe even if one regularly sunbathes in the nude by the equator!

A multivitamin supplement will provide the RDA level of 400 iu. Milk is the major dietary source because it has been fortified with vitamin D in an effort to decrease the problem of rickets / bone deformity in children. One cup (8 oz) provides 100 iu. **Until very recently there was no vitamin D in yogurt, cheese, ice cream, or in the calcium-fortified orange juice.** Now some brands are beginning to add it. Again, look VERY

closely at this one! Some people are avoiding milk, and they may be injuring themselves substantially if vitamin D is not provided optimally in some other way. The only other generous food source is salmon and tuna . . . and as with milk, one would need to eat them **frequently** to count on these foods to prevent deficiency. **Realize that one does not “have to” drink milk . . . one must simply recognize that if people drink little or no milk, they will definitely need some other reliable and generous vitamin D source . . . like a supplement.** Assuring a reasonable calcium intake from non-milk sources will also be import, of course, but the calcium need not be in the same foods or supplements as the vitamin D provided. It will be well absorbed as long as the total amount of vitamin D is adequate, regardless of the timing.

**Pending further research, if MS is diagnosed (or if it is especially severe), consider getting a one-time-only measure of 1,25-dihydroxyvitamin D level to rule out a metabolic problem converting the vitamin to its active form.** If that kind of problem is found, the individual will need a special prescription form of active vitamin D called “calcitriol.” This kind of metabolic problem has now been found in at least some people with MS.

Check that **calcium** intake is at the recommended level for age (e.g. **1000-1500 mg**). This can be especially difficult to achieve **if one is avoiding dairy foods**. In this situation (low dairy or low total calories,) a separate calcium supplement will likely be needed because most multivitamins with minerals provide only about 200 mg of calcium. **A supplement that provides vitamin D along with the calcium is a very good idea in MS and up north, even with the 400 iu of vitamin D being provided in a multivitamin.**

As a rule of thumb, (for everyone) it is a good idea to assure that the **magnesium-to-calcium** ratio is near the RDA ratio of 1-to-4. Supplementation of large amounts of calcium in the absence of adequate magnesium may increase risk of blood clots and stroke, and also bone fragility. **Magnesium is often inadequate in the diets of Americans, so make sure it isn’t inadequate in yours.** A person may need a supplement beyond a “multi with minerals” to achieve the RDA intake, depending on food choices. **The RDA for Mg is 320 mg for women and 420mg for men.** Do not take more than the RDA in supplement form without consulting your doctor. **If a person does take the RDA amount as a supplement, and then also eats magnesium-rich foods, there is still no problem.**

**Selenium** can be inadequate in low-protein diets especially, and there are other reasons (e.g geography) why many people have a poor intake. Low selenium intake has negative implications for cancer and diabetes as well as MS. An intake at 1-2 times the RDA seems reasonable for all. For example, a goal might be to provide a multi-vitamin with minerals that contains selenium (check the label) plus food content, for about **100-150 mcg total intake**. As described earlier, the RDA = 60 mcg, the upper chronic intake limit = 600 mcg , and the toxic level = 800 mcg. If the multivitamin does not provide selenium, it is easy and inexpensive to simply add a small 50 mcg tablet.

A person who follows a strictly vegetarian diet may have a **vitamin B-12** level that is seriously low. Other factors (such as a person’s age or using drugs that decrease stomach

acid) can impair absorption of vitamin B12 from food sources. Vitamin B-12 requirements may be higher than normal in MS. It is easy to provide a safe, generous, inexpensive and absorbable amount, such as the 25 mcg usually included in a “silver” type multivitamin. The RDA level = 2-3 mcg. **The crystalline form of the vitamin provided in pills does not require stomach acid for absorption the way the form in food does.**

**Folic acid availability from foods is also known to be quite variable with measurable differences in health as a result.** The best known and studied example of this is a gene called the methylenetetrahydrofolate reductase (MTHFR) gene that appears to decrease in the ability of dietary folate to do its job in preventing birth defects, depression and stroke. **This gene is especially common among people of Irish and Scots heritage (also a group at higher risk of MS,) and most people who have it are unaware that they do. However, as with vitamin B12, providing folic acid in the form found in standard vitamin pills or fortified cereals has been shown to bypass the genetic problem and make folic acid available to do its job.**

This is just one more reason why taking at least a standard multivitamin daily is a very good idea. (And remember . . . I am NOT selling anything! ☺) For one thing, **the typically recommended levels of nutrients (RDAs and RDIs, etc.) are based on the needs of the “healthy” population.** They were never intended to address the needs of people with serious health issues. The idea that a person should “just eat right” is no longer reasonable based on literally thousands of scientific studies.

**In fact, as described above, it is actually potentially harmful advice to discourage a person from taking a standard multivitamin with minerals.** Of course, a vitamin pill does not make up for a poor diet. Many important nutrients are not even provided by vitamin pills. A much more scientifically sound position today is: **“Eat right AND take a daily multivitamin with minerals.”** These are not mutually exclusive goals.

**A generous “B-complex” supplement** (e.g. “B-100”) in addition to a “multivitamin with minerals” may be helpful by raising the intake of vitamins B-6, B-12, folic acid and biotin in particular. The levels of all B-vitamins are safe at this intake level. Avoid taking more than one general “multivitamin with minerals” daily because the amount of iron, zinc and vitamin A (as retinol) may be too high.

### **Foods to Eat Less Of:**

Choose a diet generally low in:

- total fat and saturated fat,
- dairy products;
- meats that are smoked or preserved with nitrites. If you do eat cured meat, eat a vitamin C-rich food with it to decrease the formation of “nitrosamines” that are thought to contribute to cancer.

## **Foods to Eat More Of:**

Of the dietary fat consumed, generally choose fats **rich in omega-3 fatty acids (flax and especially fish)** and high in PUFAs relative to other animal fat and saturated fat.

**Supplemental EPA/DHA fish oil or flax oil capsules may be helpful**, especially if fish-eating is not desirable. The American Heart Association recommends eating fish twice a week if one has NO risk of cardiovascular disease . . . no high cholesterol, no diabetes, no family history, no smoking, etc. **However, the higher than usual free radical production and inflammation associated with MS are certainly cardiovascular risk factors on their own. For people with some cardiovascular risk, a daily fish oil capsule is suggested:**

**Recommendations for Therapeutics and Prevention. Proceedings of a symposium**, New York, New York, USA, May 21, 2005. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1451S-1538S.

**AHA Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease.** Circulation 2002;106:2747-2757

“Supplements that provide about a gram (1000 mg) of omega-3 fat daily can benefit persons with cardiovascular disease. Higher dose (2–4 grams, or 2000-4000 mg) intakes appear to greatly improve high triglyceride levels in particular. The higher doses (over 3 grams daily) should be taken only with physician approval.”

## **For EVERYONE for MANY Reasons:**

**Assure a generous antioxidant intake relative to PUFAs. If a person has MS, an even more generous intake of antioxidants is needed because of increased free radical production.** This increased need for antioxidant protection appears to be the case in many other autoimmune conditions as well, such as diabetes. Be aware that a “very low fat” diet naturally provides only minimal vitamin E as well. A good idea for all: a separate **vitamin E supplement providing 200 iu and a vitamin C supplement that provides 200-500 mg.** More may be added with a physician’s approval. Most multi-vitamins will provide only the RDA value of 30 iu of vitamin E and 60-100 mg of vitamin C. Again, the RDA levels, by definition, are based on the presumed needs of the “healthy population,” so additional consideration of specific health problems associated with MS often results in some departure from the RDA levels as a goal.

### **Aim for a generous intake of brightly colored fruits and vegetables.**

These foods are rich in nutrients and low in calories. They also provide lots of protective “phytochemicals” like lutein, lycopene, anthocyanins, carotenes, flavones, etc., which are very potent antioxidants. Other antioxidants may also be found to be helpful with new research (e.g. CoQ-10, new B-6 analogs, etc.)

## **Fourth:**

### **Troubleshooting other nutrition pitfalls for the individual with MS:**

Watch for **dysphagia** problems in MS, and assure that manipulations of food texture do not disrupt nutritional balance or add excessive calories. If eating becomes too difficult to maintain nutritional status, consider a percutaneous gastrostomy as a tool.

Good nutrition helps prevent **pressure ulcers**; but if they develop, treat with aggressive, supportive nutrition (especially generous protein and zinc, copper, and vitamin C.)

Check for potential **nutrition interaction effects of all medications**, and make nutritional adjustments as necessary. This is not just a “take with food / don’t take with food” issue.

Remember to consider **body composition and activity level** changes in assessment of nutritional status and in making recommendations for calories, etc.:

1) weight:height ratio; 2) lean body mass-to-weight ratio; and 3) activity level..

**Fifth:**

**Stay tuned for new information!**

# A COLLECTION OF ANNOTATED REFERENCES AND PARTIAL ABSTRACTS FOR THOSE WHO ARE INTERESTED:

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## **Vitamin D (2000-2007; selected annotated references)**

### **2007**

**Risk assessment for vitamin D.** Am J Clin Nutr. 2007 Jan;85(1):6-18. The objective of this review was to apply the risk assessment methodology used by the Food and Nutrition Board (FNB) to derive a revised safe Tolerable Upper Intake Level (UL) for vitamin D. New data continue to emerge regarding the health benefits of vitamin D beyond its role in bone. The intakes associated with those benefits suggest a need for levels of supplementation, food fortification, or both that are higher than current levels. A prevailing concern exists, however, regarding the potential for toxicity related to excessive vitamin D intakes. The UL established by the FNB for vitamin D (50 mug, or 2000 IU) is not based on current evidence and is viewed by many as being too restrictive, thus curtailing research, commercial development, and optimization of nutritional policy. Human clinical trial data published subsequent to the establishment of the FNB vitamin D UL published in 1997 support a significantly higher UL. We present a risk assessment based on relevant, well-designed human clinical trials of vitamin D. **Collectively, the absence of toxicity in trials conducted in healthy adults that used vitamin D dose  $\geq$ 250 mug/d (10 000 IU vitamin D(3)) supports the confident selection of this value as the UL.**

### **2006**

**Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis.** JAMA. 2006 Dec 20;296(23):2832-8. Prospective, nested case-control study among more than 7 million US military personnel who have serum samples stored in the Department of Defense Serum Repository. Multiple sclerosis cases were identified through Army and Navy physical disability databases for 1992 through 2004, and diagnoses were confirmed by medical record review. Each case (n = 257) was matched to 2 controls by age, sex, race/ethnicity, and dates of blood collection. Vitamin D status was estimated by averaging 25-hydroxyvitamin D levels of 2 or more serum samples collected before the date of initial multiple sclerosis symptoms. **Conclusion: The results of our study suggest that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis.**

**IL-10 signaling is essential for 1,25-dihydroxyvitamin D<sub>3</sub>-mediated inhibition of experimental autoimmune encephalomyelitis.** J Immunol. 2006 Nov 1;177(9):6030-7. Conclusion: Thus, 1,25-(OH)<sub>2</sub>D<sub>3</sub> may be enhancing an anti-inflammatory loop involving hemopoietic cell-produced IL-10 acting on brain parenchymal cells and vice versa. If this interpretation is correct, and humans have a similar bidirectional IL-10-dependent loop, then an IL-10-IL-10R pathway defect could abrogate the anti-inflammatory and neuro-protective functions of sunlight and vitamin D<sub>3</sub>. In this way, **a genetic IL-10-IL-10R pathway defect could interact with an environmental risk factor, vitamin D<sub>3</sub> insufficiency, to increase MS risk and severity.**

**Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases.** Anticancer Res. 2006 Jul-Aug;26(4A):2581-8. Extensive research on the CYP27B1-encoded 25-(OH)D-1alpha-hydroxylase has contributed much to our understanding about how locally produced 1,25-(OH)<sub>2</sub>D<sub>3</sub> exerts tissue-specific control of cellular growth, differentiation and function. Because many types of epithelial, mesenchymal and immune cells express the 25-(OH)D-1alpha-hydroxylase, many organ functions are necessarily affected by changes in the activity of the enzyme. It is hypothesized that this is likely to occur under conditions of hypovitaminosis D, i.e., at serum 25-(OH)D levels below 30 nM, because extra-renal 25-(OH)D-1alpha-hydroxylase activity is critically limited by the availability of its substrate. **This can provide an explanation, on a molecular and cellular basis, for the many observations that significant associations exist between a compromised vitamin D status and the pathogenesis of frequent chronic diseases. In addition to skeletal disorders, vitamin D insufficiency is a risk factor for malignancies, particularly of the colon, breast and prostate gland, as well as for chronic inflammatory and autoimmune diseases (insulin-dependent diabetes mellitus, inflammatory bowel disease, multiple sclerosis, etc.).**

**New insights into the mechanisms involved in the pleiotropic actions of 1,25dihydroxyvitamin D<sub>3</sub>.** Ann N Y Acad Sci. 2006 Apr;1068:194-203. Vitamin D functions to regulate calcium homeostasis in intestine, kidney, and bone. Vitamin D deficiency during bone development causes rickets and in adults vitamin D deficiency, which has been shown to be common in the elderly population, can cause secondary hyperparathyroidism that can result in osteomalacia and increased risk of fracture. **Recent evidence has suggested that vitamin D can have numerous other physiological functions including protection against certain autoimmune diseases, such as diabetes and multiple sclerosis and inhibition of proliferation of a number of malignant cells including breast and prostate cancer cells.** Exactly how vitamin D affects numerous different systems is a subject of continuing investigation. This article will review new developments related to the function and regulation of vitamin D target proteins in classic vitamin D target tissues that have provided novel insight into the mechanism of vitamin D action.

**Epidemiology and natural history of multiple sclerosis: new insights.** Curr Opin Neurol. 2006 Jun;19(3):248-54. PURPOSE OF REVIEW: The cause of multiple sclerosis remains elusive. We review recent epidemiological studies of genetic and environmental factors that influence susceptibility to the disease and its clinical course. RECENT FINDINGS: Genetic advances strengthen the association of multiple sclerosis with the human leukocyte antigen (HLA)-DRB1 allele and interferon-gamma polymorphisms and suggest that apolipoprotein E alleles play an important role. In the environmental realm, nested case-control studies show that prior Epstein-Barr virus exposure is overrepresented in multiple sclerosis. Smoking has been associated with both risk of multiple sclerosis and progressive disease. **Vitamin D deficiency might tie together environmental clues with higher multiple sclerosis prevalence rates; dietary vitamin supplementation is also associated with reduced multiple sclerosis risk....**

**The role of vitamin D in multiple sclerosis.** Ann Pharmacother. 2006 Jun;40(6):1158-61. OBJECTIVE: To evaluate the literature about the role of vitamin D in the prevention and treatment of multiple sclerosis (MS). DATA SOURCES: MEDLINE (1966-April 2006) and International Pharmaceutical Abstracts (1970-April 2006) searches were performed. In addition, pertinent references from identified articles were obtained. Key search terms included vitamin D, 25-hydroxyvitamin D, vitamin D deficiency, and multiple sclerosis. Data synthesis: **Vitamin D supplementation prevented the development and progression of experimental autoimmune encephalitis, an animal model of MS, in mice. A large, prospective, cohort study found that vitamin D supplementation was associated with a 40% reduction in the risk of developing MS. Four small, noncontrolled studies suggested that vitamin D supplementation may decrease exacerbation of MS symptoms.** CONCLUSIONS: **Vitamin D supplementation may help prevent the development of MS and may be a useful addition to therapy.** However, current studies are in small populations and are confounded by other variables, such as additional vitamin and mineral supplementation.

**Vitamin D and autoimmune disease--implications for practice from the multiple sclerosis literature.** J Am Diet Assoc. 2006 Mar;106(3):418-24. Recent studies and commentaries link vitamin D with several autoimmune diseases, including multiple sclerosis (MS). Adequate vitamin D intake reduces inflammatory cytokines through control of gene expression, thus inadequate vitamin D intake is suggested as a mechanism that could contribute to inflammation and, consequently, development of MS. Poor vitamin D status has been associated with increased risk for development of MS, and patients with MS may suffer consequences of vitamin D deficiency, such as bone loss. **Animal studies and very limited human data suggest possible benefit from vitamin D supplementation in patients with MS. Based on the current state of research, a key principle for practicing dietetics professionals is to include vitamin D status in nutritional assessment. For those at risk for poor vitamin D status, intake can be enhanced by food-based advice and, when indicated, vitamin D supplementation.**

[CB Note about the conclusion of the above citation – the “food-based advice” means that the vitamin D “should” be obtained from milk, salmon and some tuna. . . as there are very few other food sources. Interesting to me is the tendency for health professionals to be unaware of the fact that the vitamin D in milk is ADDED to it. It is not naturally rich in vitamin D. This kind of advice (that people “should” take their supplemental D preferentially in the form of a liquid dairy product) is not central to the fact that they simply must get enough vitamin D. Nutrition is not a religion . . . there are many ways to solve a problem. It is now known that many people require 1000-2000 iu of vitamin D daily to assure adequate levels in their blood. This is the amount provided by 10 -20 cups of milk daily . . . clearly unreasonable and also poor nutrition as there would be room for nothing else. . . Even if the milk is skim, this is rather a lot of calories (900-1800) especially for people with MS, and it obliges the displacement of other important foods. **Clearly some supplemental vitamin D must be provided in a form other than “vitamin D added to milk.” A multivitamin provides 400 iu of vitamin D. An additional amount can be obtained from an inexpensive tablet (it comes in 400 iu, 1000 iu and 2000 iu and likely other strengths will become more common. It may also be obtained from vitamin D fortified calcium pills (usually 200-400 iu) or as 100 iu per cup of milk. Please see my vitamin D handout and “Top Five” handout for specific suggestions of many ways to be sure to obtain the right amount.]**

**The photobiology of vitamin D--a topic of renewed focus.** Tidsskr Nor Laegeforen. 2006 Apr 6;126(8):1048-52. The sun is our most important source of vitamin D. Exposure to solar radiation, in sub-erythemogenic doses, also gives large amounts of this vitamin. The ultraviolet radiation in these sources converts 7-dihydrocholesterol to previtamin D3 in the skin. Furthermore, heat isomerization to vitamin D3 takes place, then transport to the liver and hydroxylation to calcidiol, which is transported to the kidneys and hydroxylated to the active hormone calcitriol. The vitamin D3 status of the body is supposed to be reliably imaged by calcidiol measurements. Calcidiol levels above 12.5 nmol/l prevent rickets and osteomalacia, but optimal levels are probably higher, in the range 100-250 nmol/l. A daily food intake of 100-200 microg vitamin D3 (50-100 g cod-liver oil), or a weekly exposure to two minimal erythemal doses of ultraviolet radiation (20 to 40 minutes whole body exposure to midday midsummer sun in Oslo, Norway), will give this level. **An adequate supply of vitamin D3 seems to reduce the incidence rates or improve the prognosis of several cancer forms, including prostate, breast and colon cancer, as well as of lymphomas. Several other diseases are related to a low vitamin D3 status: heart diseases, multiple sclerosis, diabetes, and arthritis.** The action mechanisms of vitamin D are thought to be mainly related to its known cell-differentiating and immuno-modulating effects. Even though most of the 250 annual death cases from skin cancer in Norway are caused by sun exposure, we should, in view of the health effects of ultraviolet radiation, consider modifying our restrictive attitude towards sun exposure and use of solar radiation.

[CB note on the last sentence of the above citation: Perhaps a multivitamin would be a bit safer intervention to suggest rather than ignoring the recognized risk of melanoma from sun exposure. It is also easier to do than the “weekly exposure to two minimal erythemal doses of ultraviolet radiation (20 to 40 minutes whole body exposure to midday midsummer sun in Oslo, Norway,)” especially for those of us who are shy about the whole-body exposure part.

**Vitamin D physiology.** Prog Biophys Mol Biol. 2006 Sep;92(1):4-8 . . . The active metabolite 1,25(OH)2D has an antiproliferative effect and downregulates inflammatory markers. Extrarenal synthesis of 1,25(OH)2D occurs under the influence of cytokines and is important for the paracrine regulation of cell differentiation and function. **This may explain that vitamin D deficiency can play a role in the pathogenesis of auto-immune diseases such as multiple sclerosis and diabetes type 1, and cancer.** In conclusion, the active metabolite 1,25(OH)2D has pleiotropic effects through the vitamin D receptor and vitamin D responsive elements of many genes and on the other side rapid non-genomic effects through a membrane receptor and second messengers. . . .

**Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease.** Prog Biophys Mol Biol. 2006 Sep;92(1):60-4 Autoimmune diseases like multiple sclerosis (MS) and inflammatory bowel disease (IBD) occur because of an inappropriate immune-mediated attack against self-tissue. Analyses of genetically identical twins shows that besides genetics there are

important environmental factors that contribute to MS and IBD development. **Vitamin D availability due to sunshine exposure or diet may play a role in the development of MS and IBD. Compelling data in mice show that vitamin D and signaling through the vitamin D receptor dictate the outcome of experimental MS and IBD. Furthermore, the evidence points to the direct and indirect regulation of T cell development and function by vitamin D. In the absence of vitamin D and signals delivered through the vitamin D receptor, auto reactive T cells develop and in the presence of active vitamin D (1,25(OH)(2)D(3) ) and a functional vitamin D receptor the balance in the T cell response is restored and autoimmunity avoided.**

**1,25 Dihydroxyvitamin-D3 modulates JAK-STAT pathway in IL-12/IFN $\gamma$  axis leading to Th1 response in experimental allergic encephalomyelitis.** J Neurosci Res. 2006 May 15;83(7):1299-309. ... These findings highlight the fact that vitamin D modulates JAK-STAT signaling pathway in IL-12/IFN $\gamma$  axis leading to Th1 differentiation and further **suggest its use in the treatment of MS and other Th1 cell-mediated autoimmune diseases.**

**Epidemiology of disease risks in relation to vitamin D insufficiency.** Prog Biophys Mol Biol. 2006 Sep;92(1):65-79. Vitamin D from ultraviolet-B (UVB) irradiance, food, and supplements is receiving increased attention lately for its role in maintaining optimal health. Although the calcemic effects of vitamin D have been known for about a century, the non-calcemic effects have been studied intently only during the past two-three decades. The strongest links to the beneficial roles of UVB and vitamin D to date are for bone and muscle conditions and diseases. There is also a preponderance of evidence from a variety of studies that vitamin D reduces the risk of colon cancer, with 1000 IU/day of vitamin D or serum 25-hydroxyvitamin D levels >33 ng/mL (82 nmol/L) associated with a 50% lower incidence of colorectal cancer. There is also reasonable evidence that vitamin D reduces the risk of breast, lung, ovarian, and prostate cancer and non-Hodgkin's lymphoma. There is weaker, primarily ecologic, evidence for the role of vitamin D in reducing the risk of an additional dozen types of cancer. There is reasonably strong ecologic and case-control evidence that vitamin D reduces the risk of autoimmune diseases including such as multiple sclerosis and type 1 diabetes mellitus, and weaker evidence for rheumatoid arthritis, osteoarthritis, type 2 diabetes mellitus, hypertension and stroke. It is noted that mechanisms whereby vitamin D exerts its effect are generally well understood for the various conditions and diseases discussed here.

2005

**Effects of alfacalcidol therapy on serum cytokine levels in patients with multiple sclerosis.** Srp Arh Celok Lek. 2005 Dec;133 Suppl 2:124-8 The aim of our study was to investigate the immunomodulatory effect of alfacalcidol, a vitamin D analogue, on cytokine levels in RRMS patients in relapse. ... Result: Alfacalcidol therapy in RRMS patients did not provoke any side effects. **Vitamin D and its analogues, such as alfacalcidol, act as immunomodulatory agents, with potential therapeutic effects for patients with multiple sclerosis.**

**Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis.** Med Hypotheses. 2005;64(3):608-18.... In areas of high MS prevalence, dietary supplementation of vitamin D in early life may reduce the incidence of MS. In addition, like folic acid, vitamin D supplementation should also be routinely recommended in pregnancy. Prevention of MS by modifying an important environmental factor (sunlight exposure and vitamin D level) offers a practical and cost-effective way to reduce the burden of the disease in the future generations.

**A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting multiple sclerosis.** J Neurol Neurosurg Psychiatry. 2005 Sep;76(9):1294-6. ...Conclusions: Oral calcitriol is safe and well tolerated for up to one year by diet compliant relapsing-remitting MS patients. Further study of vitamin D related mechanisms is warranted in MS.

**25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis.** Mult Scler. 2005 Jun;11(3):266-71....We conclude that the vitamin D stores in most MS patients are adequate for their normal bone metabolism. However, lower vitamin D levels during MS relapses than in remission suggest that vitamin D could be involved in the regulation of the clinical disease activity of MS. The optimal serum levels of vitamin D for the regulation of immune responses remain to be determined.

2004

**Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence.** Exp Biol Med (Maywood). 2004 Dec;229(11):1136-42. Low vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis, rheu-matoid arthritis, insulin-dependent diabetes mellitus, & inflammatory bowel disease. The optimal level of vitamin D intake required to support optimal immune function is not known but is likely to be at least that required for healthy bones. Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. ... This review discusses the accumulating evidence pointing to a link between vitamin D & autoimmunity. Increased vitamin D intakes might decrease the incidence & severity of autoimmune diseases and the rate of bone fracture.

**Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults.** J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):575-9. The physiologic range for circulating 25-hydroxyvitamin D3 [25(OH)D; the measure of Vit. D nutrient status] concentration in humans & other primates extends to beyond 200 nmol/L (>80 ng/mL). This biologic "normal" value is greater than current population norms for 25(OH)D. Concentrations of 25-(OH)D that correlate with desirable effects extend to at least 70 nmol/L, with no obvious threshold. Randomized clinical trials using 20 mcg (800 IU) per day of Vit. D show that this suppresses parathyroid hormone, preserves bone mineral density, prevents fractures, lowers blood pressure & improves balance. Calcium absorption from diet correlates with 25(OH)D in the normal range. Health effects of Vita. D beyond osteoporosis are mostly supported by the circumstantial evidence of epidemiologic studies & laboratory research. These include prevention of cancer & the auto-immune diseases, insulin-dependent diabetes & multiple sclerosis. One mcg per day of Vit. D(3) (cholecalciferol) increases circulating 25(OH)D by about 1 nmol/L (0.4 ng/mL). A recommended dietary allowance (RDA) is the long-term daily intake level that meets the total requirements for the nutrient by nearly all healthy individuals (it would presume no

sunshine). If 70 nmol/L is regarded as a minimum desirable target 25(OH)D concentration, then current recommendations of 15 mcg per day do not meet the criterion of an RDA.

**Multiple sclerosis and vitamin D: an update.** *Eur J Clin Nutr.* 2004 Aug;58(8):1095-109. ...The prevalence of MS is highest where environmental supplies of vitamin D are lowest. ... Vitamin D deficiency is caused by insufficient sunlight exposure or low dietary vitamin D(3) intake. Subtle defects in vitamin D metabolism, including genetic polymorphisms related to vitamin D, might possibly be involved as well. Optimal 25OHD serum concentrations, throughout the year, may be beneficial for patients with MS, both to obtain immune-mediated suppression of disease activity, and also to decrease disease-related complications, including increased bone resorption, fractures, and muscle weakness.

**Vitamin D intake and incidence of multiple sclerosis** *Neurology.* 2004 Jan 13;62(1):60-5. ... Dietary vitamin D intake was examined directly in relation to risk of MS in two large cohorts of women: the Nurses' Health Study (NHS; 92,253 women followed from 1980 to 2000) and Nurses' Health Study II (NHS II; 95,310 women followed from 1991 to 2001). ... **CONCLUSION: These results support a protective effect of vitamin D intake on risk of developing MS.**

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## Annotated References / Abstracts for FATS

**Polyunsaturated fatty acids and neurological diseases.** *Mini Rev Med Chem.* 2006 Nov;6(11):1201-11. This review summarizes the knowledge of the role of dietary PUFAs, especially omega-3, on normal brain function. Furthermore, it reports the **evidence pointing to potential mechanisms of omega-3 fatty acids in development of neurological disorders and efficacy of their supplementation in terms of symptom management.**

**Erythrocyte membrane fatty acids in benign and progressive forms of multiple sclerosis** *J Neurol Sci.* 2006 May 15;244(1-2):123-6. Epub 2006 Mar 6. **BACKGROUND:** There is no good explanation why a proportion of patients with multiple sclerosis (MS) have a relatively benign form of the disease. An imbalance between saturated and unsaturated fatty acids (FA) might influence the disease course of MS. **AIM:** To assess whether the erythrocyte membrane fatty acid composition, which is a biological marker of long term dietary FA consumption, is different between patients with benign and progressive MS. **METHODS:** The erythrocyte membrane FA composition was measured by gas chromatography in 23 healthy controls, 27 patients with benign MS, 32 patients with secondary progressive MS and 23 patients with primary progressive MS. None of the patients was following a special diet. **RESULTS: No significant differences in levels of saturated and unsaturated FA or in omega-3- and omega-6-polyunsaturated FA were found between controls and patients with the different subtypes of MS. Conclusion: Our data suggest that factors other than dietary fatty acid consumption are responsible for the different disease courses of MS.**

**Polyunsaturated fatty acid supplementation in MS.** *Int MS J.* 2005 Nov;12(3):88-93. This article focuses on polyunsaturated fatty acid (PUFA) supplementation, which is a popular form of complementary and alternative therapy among people with MS. Owing to their popularity, clinicians should be knowledgeable about the PUFA supplements that are widely available, and the efficacy and safety data from clinical studies. Small-scale studies have demonstrated trends towards some beneficial effects. PUFA supplementation is generally well tolerated, although some specific supplements are best avoided and some clinical situations warrant caution. A review of the efficacy and safety data suggests that PUFA supplementation may be a promising approach. Large-scale trials are required to confirm the benefits.

**Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients.** *Prostaglandins Leukot Essent Fatty Acids.* 2005 Nov;73(5):397-404. **OBJECTIVES:** To determine whether a low fat diet supplemented with omega-3 positively affects quality of life (QOL) in relapsing-remitting MS (RRMS) patients. In this 1-year long double-blind, randomized trial, patients were randomized to two dietary interventions: the "Fish Oil" (FO) group received a low fat diet (15% fat) with omega-3 FOs and the "Olive Oil" (OO) group received the AHA Step I diet (fat 30%) with OO supplements. The primary outcome measure was the Physical Components Summary Scale (PCS) of the Short Health Status Questionnaire (SF-36). Additional measures using MS specific QOL questionnaires, neurological status and relapse rate were obtained. **RESULTS:** 31 RRMS patients were enrolled, with mean follow up over 9-14 months. Clinical benefits favoring the FO group were observed on PCS/SF-36 and MHI. at 6 months. Reduced fatigue was seen on the OO diet at 6 months. **The relapse rate decreased in both groups relative to the rates during the 1 year preceding the study:** mean change in relapse rate in the FO group: -0.79 +/- SD 1.12 relapses/year vs. -0.69 +/- SD 1.11 in the OO group. **This study suggests that a low fat diet supplemented with omega-3 PUFA can have moderate benefits in RRMS patients on modifying therapies.**

**Antioxidants and polyunsaturated fatty acids in multiple sclerosis.** *Eur J Clin Nutr.* 2005 Dec;59(12):1347-61. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Oligodendrocyte damage and subsequent axonal demyelination is a hallmark of this disease. Different pathomechanisms, for example, immune-mediated inflammation, oxidative stress and excitotoxicity, are involved in the immunopathology of MS. The risk of developing MS is associated with increased dietary intake of saturated fatty acids. Polyunsaturated fatty acid (PUFA) and antioxidant deficiencies along with decreased cellular antioxidant defence mechanisms have been observed in MS patients. Furthermore, antioxidant and PUFA treatment in experimental allergic encephalomyelitis, an animal model of MS, decreased the clinical signs of disease. Low-molecular-weight antioxidants may support cellular antioxidant defences in various ways, including radical scavenging, interfering with gene transcription, protein expression, enzyme activity and by metal chelation. PUFAs may not only exert immunosuppressive actions through their incorporation in immune cells but also may affect cell function within the CNS. **Both dietary antioxidants and PUFAs have the potential to diminish disease symptoms by targeting specific pathomechanisms and supporting therapies.**

**Antioxidants in multiple sclerosis: do they have a role in therapy?** *CNS Drugs*. 2006;20(6):433-41. Multiple sclerosis (MS) is an immune-mediated disease, with inflammation and neurodegeneration contributing to neuronal demyelination and axonal injury. Current therapies for MS are directed toward modulation of the immune response; however, there is increasing evidence that oxidative stress is an important component in the pathogenesis of MS. The inflammatory environment in demyelinating lesions is conducive to the generation of reactive oxygen species. When these species are generated in MS and animal models of MS, products such as peroxynitrite and superoxide are formed that are highly toxic to cells. There are several examples of potential beneficial effects from various antioxidants in animal models of MS, but the efficacy may vary between different agents and, in some instances, may yield deleterious effects. Despite these promising results in animal models, there is limited and conflicting evidence of potential therapeutic effects of antioxidants such as vitamins C and E in treating MS. However, **clinical trials in MS patients with more potent antioxidants, identified in animal studies, have been initiated.**

**Dual effects of antioxidants in neurodegeneration: direct neuroprotection against oxidative stress and indirect protection via suppression of gli-mediated inflammation.** *Curr Pharm Des*. 2006;12(27):3521-33. Oxidative stress, in which production of highly reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms antioxidant defenses, is a feature of many neurological diseases and neurodegeneration. ROS and RNS generated extracellularly and intracellularly by various processes initiate and promote neurodegeneration in CNS. ROS and RNS can directly oxidize and damage macromolecules such as DNA, proteins, and lipids, culminating in neurodegeneration in the CNS. ... **We propose that combinations of agents which act at sequential steps in the neurodegenerative process can produce additive neuroprotective effects. A cocktail of multiple antioxidants with anti-inflammatory agents may be more beneficial in the prevention of neurodegenerative disease. A clearer appreciation of the potential therapeutic utility of antioxidants would emerge only when the complexity of their effects on mechanisms that interact to determine the extent of oxidative damage in vivo are more fully defined and understood.**

**Antioxidants and polyunsaturated fatty acids in multiple sclerosis.** *Eur J Clin Nutr*. 2005 Dec;59(12):1347-61. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Oligodendrocyte damage and subsequent axonal demyelination is a hallmark of this disease. Different pathomechanisms, for example, immune-mediated inflammation, oxidative stress and excitotoxicity, are involved in the immunopathology of MS. The risk of developing MS is associated with increased dietary intake of saturated fatty acids. Polyunsaturated fatty acid (PUFA) and antioxidant deficiencies along with decreased cellular antioxidant defence mechanisms have been observed in MS patients. Furthermore, antioxidant and PUFA treatment in experimental allergic encephalomyelitis, an animal model of MS, decreased the clinical signs of disease. Low-molecular-weight antioxidants may support cellular antioxidant defences in various ways, including radical scavenging, interfering with gene transcription, protein expression, enzyme activity and by metal chelation. PUFAs may not only exert immunosuppressive actions through their incorporation in immune cells but also may affect cell function within the CNS. **Both dietary antioxidants and PUFAs have the potential to diminish disease symptoms by targeting specific pathomechanisms and supporting recovery in MS.**

**Lipoic acid in multiple sclerosis: a pilot study.** *Mult Scler*. 2005 Feb;11(1):24-32. Lipoic acid (LA) is an antioxidant that suppresses and treats an animal model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis. ... **We conclude that oral LA is generally well tolerated and appears capable of reducing serum MMP-9 and sICAM-1 levels. LA may prove useful in treating MS by inhibiting MMP-9 activity and interfering with T-cell migration into the CNS.**

**Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis.** *J Neuroimmunol* 2002 Oct;131(1-2):104-14

**Antioxidants and polyunsaturated fatty acids in multiple sclerosis.** *Eur J Clin Nutr*. 2005 Aug 24...Both dietary antioxidants and PUFAs have the potential to diminish disease symptoms by targeting specific pathomechanisms and supporting recovery in MS.

**The role of methallothioneins in experimental autoimmune encephalomyelitis and multiple sclerosis.** *Ann N Y Acad Sci*. 2005 Jun;1051:88-96. ... In this review we summarize recent progress in understanding the regulation and function of methallothioneins during experimental autoimmune encephalomyelitis and MS. *Ann N Y Acad Sci*. 2005 Jun;1051:88-96.

**Time-course expression of CNS inflammatory, neurodegenerative tissue repair markers and metallothioneins during experimental autoimmune encephalomyelitis.** *Neuroscience*. 2005;132(4):1135-49. ... suggest that metallothionein proteins are implicated in the clinical recovery of EAE and perhaps these antioxidant proteins may provide therapeutic benefits in MS.

**Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis.** *J Immunol*. 2004 Nov 1;173(9):5794-800. ... We show that the major green tea constituent, (-)-epigallocatechin-3-gallate (EGCG), dramatically suppresses EAE induced by proteolipid protein 139-151. EGCG reduced clinical severity when given at initiation or after the onset of EAE by both limiting brain inflammation and reducing neuronal damage. ... Because its structure implicates additional antioxidative properties, EGCG was capable of protecting against neuronal injury in living brain tissue induced by N-methyl-D-aspartate or TRAIL and of directly blocking the formation of neurotoxic reactive oxygen species in neurons. Thus, a natural green tea constituent may open up a new therapeutic avenue for young disabled adults with inflammatory brain disease by combining, on one hand, anti-inflammatory and, on the other hand, neuroprotective capacities.

**Alpha lipoic acid inhibits human T-cell migration: implications for multiple sclerosis.** *J Neurosci Res*. 2004 Nov 1;78(3):362-70. We have demonstrated previously the ability of the antioxidant alpha lipoic acid (ALA) to suppress and treat a model of multiple sclerosis (MS), relapsing experimental autoimmune encephalo-myelitis (EAE). ... These data, coupled with its ability to treat relapsing EAE, suggest that ALA warrants investigation as a therapy for MS.

**Protective effects of caffeic acid phenethyl ester against experimental allergic encephalo-myelitis-induced oxidative stress in rats.** *Free Radic Biol Med*. 2004 Aug 1;37(3):386-94. ... Caffeic acid phenethyl ester (CAPE), an active component of honeybee

propolis, has been determined to have antioxidant, anti-inflammatory, antiviral, & anticancer activities. ... Treatment with CAPE significantly inhibited reactive oxygen species (ROS) production induced by EAE, & ameliorated clinical symptoms in rats. These results suggest that CAPE may exert its anti-inflammatory effect by inhibiting ROS production at the transcriptional level through the suppression of nuclear factor kappaB activation, & by directly inhibiting the catalytic activity of inducible nitric oxide synthase.

**The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy.** *J Neurol.* 2004 Mar;251(3):261-8. Accumulating data indicate that oxidative stress (OS) plays a major role in the pathogenesis of multiple sclerosis (MS). Reactive oxygen species (ROS), leading to OS, generated in excess primarily by macrophages, have been implicated as mediators of demyelination and axonal damage in both MS and experimental autoimmune encephalomyelitis (EAE), its animal model. ... treatment with antioxidants might theoretically prevent propagation of tissue damage and improve both survival and neurological outcome. Indeed, several experimental studies have been performed to see whether dietary intake of several antioxidants prevents or reduces the progression of EAE. Although a few antioxidants showed some efficacy in these studies, little information is available on the effect of treatments with such compounds in patients with MS. Well-designed clinical studies using antioxidant intake, as well as investigations based on larger cohorts studied over a longer periods of time, are needed in order to assess whether antioxidant intake together with other conventional treatments, might be beneficial in treating MS.

**Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis.** *J Neuroimmunol.* 2004 Mar;148(1-2):146-53. Alpha-lipoic acid (alpha-LA) is a neuroprotective metabolic antioxidant that has been shown to cross the blood brain barrier. We tested whether alpha-LA is capable to prevent MOG35-55-induced experimental autoimmune encephalomyelitis (EAE), an established model of multiple sclerosis (MS). ... Our data indicate that alpha-LA can effectively interfere with the autoimmune reaction associated with EAE through mechanisms other than its antioxidant activity and supports further studies on the use of alpha-LA as a potential therapy for MS.

**Bilirubin as a potent antioxidant suppresses experimental autoimmune encephalomyelitis: implications for the role of oxidative stress in the development of multiple sclerosis.** *J Neuroimmunol.* 2003 Jun;139(1-2):27-35. Increasing evidence shows that oxidative stress plays an important role in the pathogenesis of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE).

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## Annotated References / Abstracts for Vitamin B12

**Vitamin B12, folic acid, and the nervous system.** *Lancet Neurol.* 2006 Nov;5(11):949-60.

There are many reasons for reviewing the neurology of vitamin-B12 and folic-acid deficiencies together, including the intimate relation between the metabolism of the two vitamins, their morphologically indistinguishable megaloblastic anaemias, and their overlapping neuropsychiatric syndromes and neuropathology, including their related inborn errors of metabolism. Foliates and vitamin B12 have fundamental roles in CNS function at all ages, especially the methionine-synthase mediated conversion of homocysteine to methionine, which is essential for nucleotide synthesis and genomic and non-genomic methylation. Folic acid and vitamin B12 may have roles in the prevention of disorders of CNS development, mood disorders, and dementias, including Alzheimer's disease and vascular dementia in elderly people.

**Vitamin B12 and methionine synthesis: a critical review. Is nature's most beautiful cofactor misunderstood?** *Biofactors.* 2006;26(1):45-57. The mechanism by which Vitamin B12 prevents demyelination of nerve tissue is still not known. The evidence indicates that the critical site of B12 function in nerve tissue is in the enzyme, methionine synthase, in a system which requires S-adenosylmethionine. In recent years it has been recognized that S-adenosylmethionine gives rise to the deoxyadenosyl radical which catalyzes many reactions including the rearrangement of lysine to beta-lysine. Evidence is reviewed which suggests that there is an analogy between the two systems and that S-adenosyl methionine may catalyze a rearrangement of homocysteine on methionine synthase giving rise to iso- or beta-methionine. The rearranged product is readily degraded to CH<sub>3</sub>-SH, providing a mechanism for removing toxic homocysteine.

**Plasma homocysteine levels in multiple sclerosis.** *J Neurol Neurosurg Psychiatry.* 2006 Feb;77(2):189-92. **BACKGROUND:** There is evidence that homocysteine contributes to various neurodegenerative disorders, and elevated plasma homocysteine levels have been observed in patients with multiple sclerosis (MS). **OBJECTIVE:** To investigate if and why plasma homocysteine levels are increased in MS, and whether they play a role in the disease course. **METHODS:** We compared plasma levels of homocysteine in 88 patients with MS and 57 healthy controls. In the MS group, 28 had a benign course, 37 were secondary progressive, and 23 primary progressive. To explore the underlying mechanisms, we measured serum levels of vitamins B6 and B12, folate, interleukin (IL)-12, tumour necrosis factor (TNF)-alpha, leukocyte nitric oxide production, and plasma diene conjugate levels (measure of oxidative stress). **RESULTS:** Mean (SD) plasma homocysteine concentration was higher in patients (13.8 (4.9) micromol/l) than in controls (10.1 (2.5) micromol/l; p<0.0001). However, there were no significant differences in homocysteine levels between the three clinical subgroups of MS. Serum concentrations of vitamin B6, vitamin B12, and folate were not different between patients with MS and controls. In the MS group, there were no correlations between plasma homocysteine levels and the serum concentrations of IL-12 or TNF-alpha, leukocyte nitric oxide production, or plasma diene conjugate levels. **CONCLUSIONS: Elevated plasma homocysteine occurs in both benign and progressive disease courses of MS, and seems unrelated to immune activation, oxidative stress, or a deficiency in vitamin B6, vitamin B12, or folate.**

**Vitamin B12, demyelination, remyelination and repair in multiple sclerosis** *J Neurol Sci.* 2005 Jun 15;233(1-2):93-7. Multiple Sclerosis (MS) and vitamin B12 deficiency share common inflammatory and neurodegenerative pathophysiological characteristics. Due to similarities in the clinical presentations and MRI findings, the differential diagnosis between vitamin B12 deficiency and MS may be difficult. Additionally, low or decreased levels of vitamin B12 have been demonstrated in MS patients. Moreover, recent studies suggest that vitamin B12, in addition to its known role as a co-factor in myelin formation, has important immunomodulatory and neurotrophic effects. **These observations raise the questions of possible causal relationship between the two disorders, and**

**suggest further studies of the need to close monitoring of vitamin B12 levels as well as the potential requirement for supplementation of vitamin B12 alone or in combination with the immunotherapies for MS patients.**

**Attenuation of experimental autoimmune encephalomyelitis and nonimmune demyelination by IFN-beta plus vitamin B12: treatment to modify notch-1/sonic hedgehog balance.** J Immunol. 2004;172(10):6418-26. Interferon-beta is a mainstay therapy of demyelinating diseases, but its effects are incomplete in human multiple sclerosis & several of its animal models. In this study, we demonstrate dramatic **improvements of clinical, histological, & laboratory parameters in in vivo mouse models of demyelinating disease through combination therapy with IFN-beta plus vitamin B(12) cyanocobalamin (B(12)CN) in nonautoimmune primary demyelinating ND4 (DM20) transgenics, and in acute and chronic experimental autoimmune encephalomyelitis in SJL mice.** Clinical improvement (p values <0.0001) was paralleled by near normal motor function, reduced astrocytosis, and reduced demyelination. IFN-beta plus B(12)CN enhanced in vivo and in vitro oligodendrocyte maturation. In vivo & in vitro altered expression patterns of reduced Notch-1 & enhanced expression of sonic hedgehog & its receptor were consistent with oligodendrocyte maturation & remyelination. IFN-beta-B(12)CN combination therapy may be promising for the treatment of multiple sclerosis.

**Increased plasma homocysteine levels without signs of vitamin B12 deficiency in patients with multiple sclerosis assessed by blood and cerebrospinal fluid homocysteine and methylmalonic acid.** Mult Scler. 2003 Jun;9(3):239-45. Objective: The aim of this study was to evaluate if multiple sclerosis (MS) is associated with vitamin B12 (cobalamin) deficiency. Methods: We measured serum vitamin B12, plasma folate, serum methylmalonic acid (MMA), plasma homocysteine (tHcy) and also cerebrospinal fluid (CSF) MMA and tHcy in 72 patients with MS and 23 controls. Results: The mean plasma tHcy level was significantly increased in MS patients (11.6 micromol/L) compared with controls (7.4 micromol/L) (P = 0.002). Seven patients showed low serum vitamin B12 levels but only one of them had concomitant high plasma tHcy. None of them showed high serum MMA. Plasma or blood folate levels did not differ between MS patients and controls. We found no significant differences in mean values or frequency of pathological tests of serum B12, serum MMA, mean corpuscular volume (MCV), haemoglobin concentration, CSF tHcy or CSF MMA between patients and healthy subjects. There were no correlations between CSF and serum/plasma levels of MMA or tHcy. Serum vitamin B12, serum MMA, plasma tHcy, CSF tHcy or CSF MMA were not correlated to disability status, activity of disease, duration of disease or age. Conclusions: The relevance of the increased mean value of plasma tHcy thus seems uncertain and does not indicate functional vitamin B12 deficiency. We can not, however, exclude the possibility of a genetically induced dysfunction of the homocysteine metabolism relevant for the development of neuroinflammation/degeneration. Our findings indicate that, regardless of a significant increase in plasma tHcy in MS patients, the MS disease is not generally associated with vitamin B12 deficiency since we did not find any other factors indicating vitamin B12 deficiency. Analysis of CSF MMA and CSF tHcy, which probably reflects the brain vitamin B12 status better than serum, are not warranted in MS. **We conclude that B12 deficiency, in general, is not associated with MS.**

**Lipoprotein oxidation, plasma total antioxidant capacity and homocysteine level in patients with multiple sclerosis.** Nutr Neurosci. 2003 Jun;6(3):189-96. Free radical-mediated peroxidation of biological molecules, especially of lipids, is implicated in the pathogenesis of a number of diseases like multiple sclerosis. **Low concentration of antioxidant vitamins: beta carotene, retinol, alpha tocopherol and ascorbic acid have been observed in serum or cerebrospinal fluid of multiple sclerosis patients.** On the basis of these observations, we studied the potential lipoprotein oxidation and total antioxidant capacity in the pathogenesis of multiple sclerosis. Lipoprotein oxidizability for plasma in vitro, serum levels of autoantibodies against oxidized low-density lipoproteins, plasma total homocysteine levels with vitamin B12 and folate, and plasma total antioxidant capacity were measured in twenty four patients with multiple sclerosis and twenty four healthy sex- and age-matched person as control. In multiple sclerosis patients during an attack, a significant increase in both in vitro lipid oxidizability for plasma and in the levels of autoantibodies against oxidized low-density lipoproteins, and a strong decrease in plasma total antioxidant capacity were detected. **Plasma total homocysteine levels were significantly higher in multiple sclerosis patients whose plasma vitamin B12 and folate levels were lower but not statistically significant, than controls. The present study indicates that lipoprotein oxidation may be important factor in the course of multiple sclerosis and in vitro measurements of plasma oxidation kinetics as an indication for lipoprotein oxidation might be useful as an additional tool for the clinical diagnosis of multiple sclerosis.**

**Treatment of multiple sclerosis with lofepramine, L-phenylalanine and vitamin B(12): mechanism of action and clinical importance: roles of the locus coeruleus and central noradrenergic systems.** Med Hypotheses. 2002 Nov;59(5):594-602. In a randomized, placebo-controlled double-blind trial **a combination of lofepramine, phenylalanine and vitamin B(12) was found to be effective in relieving the symptoms of multiple sclerosis (MS).** The effect occurred within 2-4 weeks, and improved all types of symptoms in all types of MS. The combination was also effective in relieving symptoms in patients with chronic pain and chronic fatigue. We hypothesize that the action of this combined therapy may relate to activation of the noradrenergic locus coeruleus/lateral tegmentum (LC/LT) system which has the potential to influence the functioning of large areas of the brain and spinal cord.

**A randomised placebo controlled exploratory study of vitamin B-12, lofepramine, and L-phenylalanine (the "Cari Loder regime") in the treatment of multiple sclerosis.** J Neurol Neurosurg Psychiatry. 2002 Sep;73(3):246-9 OBJECTIVE: To determine whether combination therapy with lofepramine, L-phenylalanine, and intramuscular vitamin B-12 (the "Cari Loder regime") reduces disability in patients with multiple sclerosis. METHODS: A placebo controlled, double blind, randomised study carried out in five United Kingdom centres on outpatients with clinically definite multiple sclerosis, measurable disability on Guy's neurological disability scale (GNDS), no relapse in the preceding six months, and not on antidepressant drugs. Over 24 weeks all patients received vitamin B-12, 1 mg intramuscularly weekly, and either lofepramine 70 mg and L-phenylalanine 500 mg twice daily, or matching placebo tablets. Outcome was assessed using the GNDS, the Kurtzke expanded disability status scale; the Beck depression inventory, the Chalder fatigue scale, and the Gulick MS specific symptom scale. RESULTS: 138 patients were entered, and two were lost from each group. There was no statistically significant difference between the groups at entry or at follow up. Analysis of covariance suggested that treated patients had better outcomes on four of the five scales used. Both groups showed a reduction of 2 GNDS points within the first two weeks, and when data from all time points were considered, the treated group had a significant improvement of 0.6 GNDS points from two weeks onwards. CONCLUSIONS: **Patients with multiple sclerosis improved by 2 GNDS points after starting vitamin B-12 injections. The addition of lofepramine and L-phenylalanine added a further 0.6 points benefit. More research is needed to confirm and explore the significance of this clinically small difference.**