

## Multiple Sclerosis

Multiple sclerosis (MS) is an often debilitating (and sometimes fatal) neurological disorder that strikes more than a quarter of a million people in the United States each year (Noonan CW et al 2002). The symptoms of MS often first appear in early adulthood and can include numbness, impaired vision, weakness, loss of balance, and bladder dysfunction. Fatigue is a common early symptom. Depression is more common in people who have MS than in the general population (Patten SB et al 1997). In recent years, scientists have made dramatic advances in understanding and treating this enigmatic disease.

### WHAT IS MS?

The term multiple sclerosis refers to the numerous sclerotic lesions, or scars, that form on nerve cells. MS results from progressive damage to the myelin sheathing that insulates and protects nerve cell axons. Axons are the long, thin structures that transmit electrical impulses along the length of individual nerves, before propagating the impulse across a synapse to the next neuron. Like electrical wires, axons are encased in a nonconductive sheathing. In the case of neurons, this insulation consists of a white fatty substance known as myelin.

For reasons that remain a mystery, the immune systems of people who have MS attempt to destroy the body's own myelin. Specifically, a type of white blood cell called a T-cell becomes sensitized against myelin self-antigens. These sensitized T-cells secrete various inflammatory mediators (including tumor necrosis factor, cytokines, and prostaglandins) that eventually strip away myelin and damage supportive cells, thereby incapacitating or destroying the axon (Kidd PM 2001). MS is thus an inflammatory autoimmune demyelinating disease.

Symptoms affecting mobility tend to appear early in the course of MS. They may include sensations of heaviness, weakness, clumsiness, leg dragging, stiffness, and a tendency to drop objects. Sensory symptoms may include numbness, tingling, and electrical sensations. Visual symptoms (such as blurred, double, or foggy vision; eyeball pain; and even blindness) may appear early in the course of the disease. Visual symptoms afflict more than one-third of all people who have MS. If MS affects the nerves that supply the vestibular apparatus in the ears, the person with MS will experience dizziness, nausea, and vomiting. In the later stages of the disease, involvement of the genitourinary tract may result in loss of bladder, sexual, and bowel function (Hartung HP et al 2004; Kidd PM 2001).

Symptoms may come and go for more than 30 years, and the rate of disease progression varies markedly from one person to another. But studies indicate that, in about half of all patients, the disease will inexorably progress towards severe disability or premature death (Kidd PM 2001). The inherent unpredictability of the disease has prompted some scientists to propose that MS is not a single disease at all. Rather, they postulate, it falls within a spectrum of disorders, characterized as inflammatory demyelinating diseases of the central nervous system (Weinshenker BG 1995).

### WHAT CAUSES MS?

While it's unclear exactly what causes MS, researchers have made progress in understanding the underlying chemical reactions that occur during MS. In recent years, nitric oxide has been implicated in the development of MS. In the vascular system, nitric oxide acts as a dilator, expanding arterial walls and lowering blood pressure. In the central nervous system, however, nitric oxide generates free-radical byproducts that contribute to myelin destruction and the loss of nerve function (Smith KJ et al 2002). The picture is complicated, however, by the fact that nitric oxide also has good effects in MS, including modulating the immune system (Smith KJ et al 2002). Studies hoping to manipulate nitric oxide production have yielded mixed results in people who have MS. Research is ongoing.

Researchers have identified a number of factors that are associated with MS. It is unlikely that MS has any single cause. Rather, it appears that a multitude of factors likely work together to trigger and exacerbate the disease. These include:

**Genetic disorders.** Studies examining the incidence of the disease in the general population, in families, and in twins support a genetic component to MS (Willer CJ et al 2000). However, no single gene has been identified that determines susceptibility to the disease; rather, a number of genes are believed to be involved. About one quarter of all people who have MS have a relative who is also afflicted with the disease

Studies of identical twins show that MS occurs in both twins in about 25 percent to 35 percent of cases. This finding suggests that up to 75 percent of MS must be attributable to nongenetic factors and that the contribution of genetics is actually relatively minor (Willer CJ et al 2000, 2003). It appears that, in addition to genetically predisposing factors, external triggers must be encountered in

order for the disease to be initiated. These triggers activate the immune system to identify myelin as a nonself molecule and sets in motion the inflammatory cascade that ultimately ends in destruction of the myelin sheath.

**Infectious agents.** Various infectious agents have been proposed as triggers for MS. There is significant data that infection is involved in both the initiation of the disease and in damage to the nerves (Steiner I et al 2001). Several organisms have been proposed as potential triggers, including human herpesvirus type 6, *Mycoplasma pneumoniae*, and the relatively common primitive bacterium *Chlamydia pneumoniae*, among others. In addition, virtually all people who have MS are infected with the Epstein-Barr virus, which is widespread in the general population. Epstein-Barr virus causes the childhood illness infectious mononucleosis (Alotaibi S et al 2004; Munch M et al 1997). Some researchers believe that a dual infection with a retrovirus and the Epstein-Barr virus may serve as a trigger (Haahr S et al 2000).

**Environmental toxins.** Exposure to chemical toxins, such as organic solvents and pesticides, has been suggested as another possible MS trigger. Similarly, exposure to heavy metals, such as mercury, has been implicated in MS. Mercury is believed to be one of the most toxic of all nonradioactive elements; it is widely known to affect neurological tissue (Mutter J et al 2005). Recently, researchers in the Czech Republic removed mercury-containing amalgam dental fillings from patients who had autoimmune diseases, including MS. On follow-up, the patients who had MS in particular experienced an improvement in their symptoms after the procedure. This suggests that mercury, which is known to leach out of such fillings, may play an adverse role in the disease (Prochazkova J et al 2004). Other studies have also found a possible link between mercury exposure from dental fillings and the incidence of MS. This idea is controversial because there is also data supporting the position that mercury from dental amalgam fillings is not a health threat (Bates MN et al 2004; Sibling RL et al 1994).

**Organic solvents.** In the mid 1990s, researchers in Sweden evaluated 13 studies on the connection between solvent exposure and autoimmune disease between 1966 and 1994. Organic solvents include chemicals such as toluene, paint thinner, and acetone, the latter of which is commonly found in nail polish remover. Ten of those studies indicated a significant relationship between organic solvent exposure and MS. All the analyses suggested that exposure to solvents increases a person's relative risk of developing MS (Landtblom AM et al 1996).

More recently, a team of scientists in Norway analyzed the occupational health records of more than 57,000 workers in their country, covering a 16-year period. They concluded that workers (such as painters) who were routinely exposed to organic solvents had a significantly greater incidence of MS than men and women who were not occupationally exposed to solvents. These results were compatible with the hypothesis that organic solvents are a possible risk factor for MS (Riise T et al 2002).

## MS AND FOOD ALLERGIES

Allergies to certain foods may also play a role in the development or exacerbation of MS. MS is most prevalent in areas where consumption of wheat gluten and milk are also high. Gluten and milk are common food allergens (Butcher J 1976; Kidd PM 2001). This relationship has not been proven conclusively, but allergies may play some role in the onset or severity of MS. Components of some foods may act as triggers to the immune system, causing it to begin an inappropriate autoimmune response similar to the body's autoimmune response to bacteria and viruses.

Milk has long been suspected to play a role in the development of MS. Researchers in France examined epidemiological data from populations around the world and found a highly significant correlation between consumption of liquid cow's milk and the prevalence of MS. Interestingly, they discovered a weaker correlation between MS and the consumption of butter and cream, and no correlation between MS and cheese consumption (Malosse D et al 1992). While it's been demonstrated that saturated fat, which is relatively high in whole milk products, is harmful to people who have MS, there may be more to the dairy connection than mere fat. One of the proteins in milk mimics a particular protein affiliated with human myelin. This milk protein could easily trigger an autoimmune response to native myelin, triggering an MS episode. Indeed, this immunologic cross-reactivity has been demonstrated in the laboratory in rodents that have MS (Guggenmos J et al 2004; Stefferl A et al 2000).

Apart from specific cross-reactions to food proteins, a majority of patients who have MS reportedly have a variety of digestive system deficits, including poor digestive enzyme production, poor digestion of fats and proteins, and suboptimal absorption of various nutrients, including vitamin B12 (Lauer K et al 1986). Certain bacteria, notably *Lactobacillus* species, are helpful and necessary symbionts; their presence benefits the digestive process. Along with other beneficial bacteria, they constitute the normal gut microflora. Other microorganisms, such as the fungus *Candida albicans*, may be characterized as pest organisms capable of upsetting the delicate balance of the normal microflora. At least one researcher has reported that some patients who have MS who were treated for yeast infections—and who subsequently had their gut microflora recolonized with friendly probiotic organisms (such as those present in active yogurt cultures)—experienced significant improvement in their MS symptoms (Kidd PM 2001; Wright JV 1997).

## CONVENTIONAL MS TREATMENT

Current first-line treatments for MS include a number of drugs designed to influence the immune system to slow or halt inflammation

and destruction of myelin or inhibit nitric oxide. Recent years have brought dramatic advances in treatment, but substantial room for improvement remains. None of the drugs available today rise above a partially effective designation. While drug therapies may reduce the severity and frequency of symptoms, a complete cure remains as elusive as ever.

The drugs usually used to treat MS flare-ups are corticosteroids such as prednisone. These drugs are often prescribed for short periods to alleviate the main symptoms of MS. Studies have shown that the corticosteroids inhibit creation of nitric oxide in the central nervous system (Lieb K et al 2003) in addition to their other, well-known, anti-inflammatory effects such as reduction of cytokine formation and immune cell function. They should not be used for long-term therapy, however, because of their many side effects, including increased risk of infection, weight gain, fatigue, diabetes, osteoporosis, personality changes (including psychosis), and ulcers. Also, while corticosteroids may reduce the symptoms of the disease, they have no effect on its progression.

The US Food and Drug Administration has approved the immune system–modulating drugs interferon  $\beta$ -1b, interferon  $\beta$ -1a, and glatiramer acetate for the first-line treatment of relapsing forms of MS (Miller DH et al 2003; Noseworthy JH 1998). Additional cutting-edge treatments include humanized monoclonal antibodies such as daclizumab and alemtuzumab; oral immunomodulators such as sirolimus; cholesterol-lowering statins; estrogens; neuroprotective agents such as NMDA antagonists; the phosphodiesterase inhibitor ibudilast; and sodium-channel blockers, among others (Chofflon M 2005; Farrell R et al 2005; Feng J et al 2004; Miller DH et al 2003; Murdoch D et al 2005; Polman CH et al 2003).

Some of these drugs have been used in combination to reasonably good effect (Vollmer TL et al 2004). Although immunoglobulin G is not considered first-line therapy, some clinicians use it to treat symptoms of MS (Sorensen PS et al 2002). Monoclonal antibodies, such as natalizumab, constitute a new generation of immunosuppressants that act on immune-cell surface ligands. Ligands are the portions of molecules responsible for binding with other molecules, as in the interaction between an antibody and its antigen. The monoclonal antibodies offer relatively focused immunosuppressive actions, and somewhat better safety profiles, compared to conventional immunosuppressants (Chofflon M 2005). Both the monoclonal antibodies and immunoglobulin treatments are very expensive and, because they are human proteins, there is a risk of serious allergic reaction.

Many of the medications have serious side effects, so the benefits must be considered along with the risks before treatment. Mitoxantrone is a broad-spectrum immunosuppressant primarily used as a cancer chemotherapy agent. It is occasionally prescribed to treat MS, especially in cases of progressive disease. But its side effects—which include possible heart damage and potential induction of leukemia—render it less than ideal, especially for long-term use. Pentoxifylline is another drug that offered promise initially, but results from subsequent clinical studies have been disappointing (Prieto JM et al 2001).

### ***What You Have Learned So Far***

- MS is an autoimmune disorder in which a person's immune system attacks the myelin sheath that protects nerve cells. Eventually, this sheath can be destroyed.
- MS is a highly variable disease that affects different people differently. Some people may experience subclinical MS that does not progress, while others will experience a debilitating form of the disease that results in loss of mobility and possible death.
- MS tends to have a variable course, with exacerbations occurring at irregular intervals.
- The cause of MS is unknown, although it is most likely due to multiple factors, including genetics, exposure to toxins, infectious agents, diet, and, possibly, allergies.
- There is no single drug used to treat MS. Instead, most physicians rely on drugs that suppress the autoimmune reaction and protect the myelin sheath in a variety of ways. Some of these drugs have serious side effects.

## **VITAMIN D DEFICIENCY: AN MS RISK FACTOR**

Vitamin D is emerging as a far more important immune system component than was previously appreciated. Long known to play a key role in the regulation of calcium and in the formation and maintenance of healthy bones, vitamin D is now known to influence cell differentiation, function, and survival (Montero-Odasso M et al 2005). In fact, the most bioactive form of vitamin D acts as a hormone in the body, and receptors for it have been discovered in a wide range of tissues.

Vitamin D may also be involved in preventing MS. This was originally inferred from epidemiological data. Scientists noted that MS is more prevalent in people living at higher latitudes (in either the Northern or Southern hemispheres) where sunlight is weaker, particularly in winter. The most bioactive form of vitamin D is generated in the body through a biosynthetic process that begins with, and is dependent on, exposure of the bare skin to sunlight.

In 2004, scientists from the Harvard School of Public Health published the results of two long-term studies on women's health and nutrition. Researchers looked at dietary and supplemental intake of vitamin D as it related to the incidence of MS. Gleaned from the Nurses' Health Study (more than 92,000 women followed from 1980 to 2000) and the Nurses' Health Study II (more than 95,000

women followed from 1991 to 2001), the data support a protective effect for vitamin D against MS, especially for women who consume more than 400 international units (IU) daily of vitamin D from supplements, but not from food sources (Munger KL et al 2004).

Scientists now believe that vitamin D (commonly depleted in people who have MS) may play a crucial role in preventing the disease (Ponsonby AL et al 2005a; Wingerchuk DM et al 2005). Low vitamin D levels are also an emerging risk factor for other diseases and disorders such as type 1 diabetes, heart disease, and rheumatoid arthritis (Holick MF 2005; Merlino LA et al 2004; Munger KL et al 2004; Ponsonby AL et al 2002; Ponsonby AL et al 2005b).

The optimal level of vitamin D varies, but many experts agree that supplemental vitamin D is required, even up to 1000 IU daily (Holick MF 2005). By contrast, a whole-body exposure to peak summer sun will rapidly cause the release of up to 20,000 IU into the circulation (Hollis BW 2005). Other experts suggest that anyone with a blood level of less than 80 nanomoles per liter (nmol/L) of circulating 25-hydroxyvitamin D is at risk of a vitamin D deficiency (Hanley DA et al 2005; Hollis BW 2005).

## **VITAMIN D AND CALCITRIOL'S BENEFITS**

In addition to reducing the risk of developing MS, supplemental vitamin D may also provide relief for those actively afflicted with the disease, at least in part by inhibiting nitric oxide, according to animal studies (Garcion E et al 2003). A small clinical trial conducted at the Mayo Clinic was designed to assess the safety and tolerability of daily use for a year of calcitriol, a prescription drug form of vitamin D. Patients who enrolled in the trial were diagnosed with relapsing-remitting MS. Patients received an equivalent of 2.5 micrograms per day (mcg/day) of calcitriol (about 100 IU/day), while their dietary calcium was restricted to 800 milligrams per day (mg/day). Researchers concluded that oral calcitriol is safe and well tolerated by patients with MS who comply with dietary recommendations (Wingerchuk DM et al 2005).

Scientists have also discovered that vitamin D effectively blocks development of MS in animals. When the biologically active, hormone form of vitamin D was administered to animals in a laboratory, the disorder was prevented. Conversely, a deficiency of vitamin D tended to increase the animals' susceptibility to the induced disease. When animals were given vitamin D after developing the disease, progression of symptoms was blocked. When vitamin D supplementation was withdrawn, the disease resumed (Cantorna MT et al 1996, 2000). Numerous laboratories have replicated and expanded upon these findings, prompting one researcher to declare: "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 future generations" (Chaudhuri A 2005).

## **HORMONE IMBALANCES AND MS**

In recent years, researchers have made great progress understanding how hormone status affects autoimmune disorders, including MS. Numerous studies have observed that MS is more common in women, and that the disease course is affected by the normal ebb and flow of steroid hormones during a woman's monthly menstrual cycle (Pozzilli C et al 1999). Interestingly, it is also well known that pregnancy tends to neutralize the disease course, or even positively affect it, enabling women who have MS to bear children safely (Hughes MD 2004).

These findings point to the important role of steroid hormones in influencing the course of the disease. This theory makes even more sense considering that sex steroid hormones such as estrogen, testosterone, progesterone, and dehydroepiandrosterone (DHEA) are known to have immunomodulatory effects. Hoping to better understand the role of hormones in MS, a number of researchers have conducted studies. Their findings include:

- In a study on rats, researchers found that animals given progesterone alone experienced greater motor defects and inflammation than rats treated with estrogen. The negative effects of progesterone were negated when estrogen was added (Hoffman GE et al 2001).
- Administering estrogen (including estriol and beta-estriol) along with progesterone was shown to inhibit production of nitric oxide in central nervous system cells. This effect was enhanced when the levels of estrogen and progesterone were maintained at levels found during late pregnancy (Drew PD et al 2000).
- Estriol treatment significantly reduced disease severity in animals with MS, while treatment with progesterone had no effect. Administering estriol until treatment levels reached levels consistent with those in late pregnancy completely ameliorated the disease (Kim S et al 1999).
- During a human study that examined the presence of MS lesions by magnetic resonance imaging (MRI), patients with high estradiol and low progesterone levels had more lesions than those who had low levels of both hormones, while patients with a high estrogen to progesterone ratio had a significantly greater number of active lesions than patients who had a low ratio (Bansil S et al 1999).

Obviously, these studies point to a conflict in our understanding of the role hormones play in MS. Animal studies have tended to show progesterone as neutral, while estrogen seems to have a protective effect. In people, however, a high ratio of estrogen to progesterone was associated with more MS lesions. Accordingly, there is a great deal of debate among researchers about the

possible role of hormones in MS therapy. Some studies (aimed at maintaining levels of estrogen to progesterone that are consistent with late pregnancy) have argued in favor of treating women with MS with bioidentical hormone replacement therapy. Other studies note that pregnant women who have MS tend to experience a rebound of their disease the first 3 months after delivery (El-Etr M et al 2005). According to a recent review, more studies are needed to determine the exact relationship between MS and hormonal imbalances (Trenova AG et al 2004).

DHEA also deserves attention in people of both sexes who have MS. DHEA is a steroid hormone. Altered levels of DHEA have been associated with various autoimmune diseases and their symptoms, including MS (Calabrese VP et al 1990). One study found that people with MS have relatively lower DHEA levels compared to healthy control subjects and that, at least in animals, DHEA therapy reduces T-cell proliferation, secretion of pro-inflammatory chemicals, and nitric oxide synthesis (Du C et al 2001; Offner H et al 2002; Ramsaransing GS et al 2005). Similarly, researchers have found that people with MS have a higher ratio of cortisol (the body's main stress hormone) to DHEA than do healthy control subjects, although this is probably a symptom of the disease rather than a causal factor (Kumpfel T et al 1999).

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Besides hormone therapy, a number of dietary factors may also play a role in decreasing the risk of developing MS or reducing the severity of symptoms. The most striking of these appears to be dietary fat.

In 1991, the results of a 34-year study conducted on patients with MS were published. Between 1949 and 1984, 150 patients were directed to consume low-fat diets. Their intake of proteins, fats, and oils was documented, and subsequent disabilities and deaths were noted. The research team found that people who consumed a low-fat diet had less disease progression and increased survival than their counterparts who ate a higher-fat diet (Swank RL 1991).

The link between MS and the types and amount of dietary fats consumed has also been established through epidemiological analysis. A high or increased intake of saturated fats, animal fats, and dairy products (another source of saturated fats, except in the case of low-fat dairy products) is associated with an increased risk of developing MS (Agranoff BWA et al 1974; Lauer K 1997; Schwarz S et al 2005; van Meeteren ME et al 2005).

Conversely, evidence shows that a higher consumption of polyunsaturated fatty acids, including omega-6 and especially omega-3 fatty acids, is associated with a decreased risk of MS and slower disease progression in people who have milder forms of the disease (Agnello E et al 2004; Bates D 1990; Swank RL et al 1990; Swank RL 1991; Zhang SM et al 2000). In fact, increased consumption of specific polyunsaturated fatty acids, such as long-chain omega-3 fatty acids, may moderate the course of the established disease. Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in relatively high amounts in cold water fish and dietary supplements (Agnello E et al 2004; Ferrucci L et al 2005; Nordvik I et al 2000; Shapiro H 2003).

Recently, researchers discovered that omega-3 fatty acids serve as precursors for newly described anti-inflammatory compounds, called docosatrienes and neuroprotectins, while simultaneously reducing the autoimmune response found in MS (Bannenberg GL et al 2005; Harbige LS et al 2001; Serhan CN 2005a,b; Serhan CN 2004).

A small, randomized, double-blind study investigated the effects of dietary fat consumption on the course of disease in patients who have relapsing-remitting MS. Researchers found that a low-fat diet supplemented with omega-3 fatty acids had moderate benefits in terms of physical components of health status and quality of life. Patients also experienced lower relapse rates while on the supplemented diet than they did in the preceding year (Weinstock-Guttman B et al 2005).

### NUTRITIONAL APPROACHES TO MS

In addition to adequate vitamin D intake and maintaining a proper balance between omega-3 and omega-6 fatty acids, a number of other nutrients have been studied in the context of MS. These include:

**Linoleic and gamma-linolenic acids.** Linoleic acid is an essential omega-6 fatty acid. At least one research team has reported that some patients who have MS have abnormally low levels of this nutrient (Homa ST et al 1981). The results of several double-blind, placebo-controlled clinical trials of linolenic acid supplementation for the treatment of MS were evaluated by meta-analysis. The conditions of 87 patients with MS and 85 normal control subjects were assessed for neurological changes over 2.5 years. Patients with low levels of disability at the beginning of the study had a smaller increase in disability over the study period than did the control subjects. In addition, linoleic acid was found to reduce the severity and duration of MS episodes in patients at all levels of the disease (Dworkin RH et al 1984).

In the body, linoleic acid is converted to gamma-linolenic acid (GLA), another omega-6 fatty acid. But this conversion is occasionally interrupted or inhibited, especially in inflammatory disease states such as diabetes and atopic dermatitis (Horrobin DF 1997, 2000; Jamal GA 1994; Kidd PM 2001). Defects in conversion may have a genetic basis, which is thought to predispose some people to inflammatory conditions (Horrobin DF 2000). GLA quells inflammation by competing with pro-inflammatory arachidonic acid. In animals with MS, GLA-fed animals fared significantly better than did control animals (Harbige LS et al 2000).

**Antioxidants.** Patients who have MS tend to have abnormally low levels of certain key antioxidants, such as glutathione peroxidase (Mai J et al 1990; Mazzella GL et al 1983; van Meeteren ME et al 2005). Supplemental antioxidants support cellular antioxidant defenses by scavenging free radicals; reducing inflammatory cell responses by interfering with gene transcription, protein expression, and enzyme activity; and by chelation of metals. Antioxidant therapy in animals with MS have yielded decreases in clinical signs of the disease (van Meeteren ME et al 2005).

In Denmark, researchers conducted a small study in which patients with MS were given an antioxidant mixture containing 6 mg of sodium selenite (equivalent to 2740 micrograms of elemental selenium), 2 grams of vitamin C, and 480 mg of vitamin E, once a day for 5 weeks. Although glutathione peroxidase levels were initially lower in patients with MS than in normal control subjects, after 5

weeks of antioxidant therapy, levels of this antioxidant increased 5-fold; side effects were minimal (Mai J et al 1990). This is an important demonstration of the ways in which supplements can help boost the body's own antioxidant mechanisms.

Although glutathione is available in supplement form, it is poorly absorbed. A better strategy for increasing the body's supply of glutathione is taking the oral supplement N-acetylcysteine (NAC), a potent antioxidant that serves as a precursor to glutathione (Arfsten D et al 2004; Kidd PM 2001). NAC has been shown to increase depleted levels of glutathione. While its specific use in the treatment of MS has not been investigated, its theoretical usefulness in the treatment of the disease has been noted by some researchers (Kidd PM 2001; Singh I et al 1998). In animals with MS or related diseases, NAC has been shown to reduce nitric oxide production in brain-supporting tissues and reduce clinical symptoms and microscopic evidence of brain cell injury and inflammation (de Bustos F et al 2000; Gilgun-Sherki Y et al 2005; Syburra C et al 1999).

Coenzyme Q10 (CoQ10) is another antioxidant of potential usefulness in treating MS and, while there is some debate, its levels may be low in patients with MS (Syburra C et al 1999). Although CoQ10 has not been investigated specifically for the treatment of MS, it is generally recognized as safe, well tolerated, and potentially useful in the treatment of neurodegenerative disorders. CoQ10 is a naturally occurring, lipid-soluble antioxidant that serves as a co-factor in the mitochondrial respiratory chain. Mitochondria are subcellular organelles present in all cells; they are responsible for the production of cellular energy. As an added bonus, CoQ10 is capable of regenerating the antioxidant capacity of spent vitamin E in the body. Decreased levels of CoQ10 are associated with many disease states, including heart disease, cancer, and neurodegenerative diseases (Bonakdar RA 2005; Siemieniuk E et al 2005).

**Lipoic acid.** Lipoic acid has been studied specifically in MS. Known to cross the blood-brain barrier and to penetrate cellular mitochondria, lipoic acid decreases the activity of intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is a small molecule that plays a role in the genesis of MS. It is believed that ICAM-1 and other adhesion molecules are responsible for allowing certain pro-inflammatory immune system cells, namely T-lymphocytes, to cross the blood-brain barrier, paving the way for induction or exacerbation of damage to neurons (Biernacki K et al 2004; Cournu-Rebeix I et al 2003; Dedrick RL et al 2003).

In experiments on rodents with MS, lipoic acid produced significant reduction of demyelination and reduced the infiltration of inflammatory T-cells across the blood-brain barrier (Marracci GH et al 2002, 2004; Morini M et al 2004).

Other teams have followed up on these studies. A research team recently published the results of a small clinical trial of lipoic acid in the treatment of patients with MS. Thirty-seven patients with MS were randomly assigned to receive various doses of lipoic acid (up to 2400 mg/day) or placebo. After just 2 weeks, patients were assessed for levels of ICAM-1, and tolerability of high-dose lipoic acid was also evaluated. Lipoic acid was generally well tolerated and reduced ICAM-1 levels, as well as interfered with T-cell migration into the central nervous system (Yadav V et al 2005).

**Vitamin B12.** Vitamin B12 plays a key role in the generation of myelin. Studies have shown that patients with MS often have abnormally low levels of vitamin B12 in their cerebrospinal fluid and/or blood serum (Reynolds EH 1992). In fact, clinical vitamin B12 deficiency and MS share remarkably similar characteristics, occasionally rendering correct diagnosis difficult (Miller A et al 2005). For more than three decades, many physicians have prescribed vitamin B12 injections for patients who have MS. Patients who have received vitamin B12 supplements have reportedly experienced consistent clinical improvements in their symptoms (Kidd PM 2001).

In the United Kingdom, researchers investigated the effects of 6 months of vitamin B12 injections (1 mg/week) on 138 patients with MS, in a double-blind, placebo-controlled, randomized study. Patients were assessed using a standardized evaluation of neurological disability. Although the treatment regimen also included the eventual addition of two other compounds, the researchers concluded that the conditions of patients with MS improved after starting vitamin B12 injections (Wade DT et al 2002).

### **ADDITIONAL CONSIDERATIONS: EXCESSIVE HEAT**

Many patients with MS report that their condition is exacerbated by overheating. This is unfortunate, as exposure to sunlight increases vitamin D naturally, and vitamin D may be helpful in the context of MS. It is ironic that many patients with MS deliberately avoid exposure to sunlight because they associate the warming rays of the sun with aggravated symptoms. Evidence suggests that patients with MS do not regulate body temperature normally (Smith KJ et al 1999). As a result, sunbathing or immersion in hot tubs may elevate core body temperature while triggering symptoms. In extreme cases, this has led to the deaths of patients who experienced muscle weakness and died when they were unable to escape the source of the heat (Henke AF et al 2000; Kohlmeier RE et al 2000). Clearly, patients with MS should not use hot tubs or elevate their body temperature excessively.

### **LIFE EXTENSION FOUNDATION RECOMMENDATIONS**

Recent advances in the understanding and treatment of MS have improved the prognosis and quality of life of MS patients. People with MS have a substantial ability to affect the course of their illness. By adhering to a proper diet; avoiding toxins (such as solvents or heavy metals) and known triggers; getting mild, regular exercise; taking recommended supplements; and working with qualified physicians, it is possible to positively affect the course of this frustrating disease.

Supplements that have been studied in animals and people with MS include:

- **Vitamin D**— 1000 international units (IU) daily
- **EPA/DHA**—3000 to 4000 milligrams (mg) daily of fish oil concentrate
- **GLA**— 1000 to 3000 mg daily of high GLA oil
- **DHEA**— 15 to 75 mg daily (Have blood tested in 3 to 6 weeks to maintain optimal levels.)
- **NAC**— 600 mg daily with 1800 mg of vitamin C
- **Vitamin E**— 400 IU daily
- **CoQ10**— 100 to 300 mg daily
- **Lipoic acid (preferably R-dihydro lipoic acid)**—300 mg daily
- **Vitamin B12**— 5 to 40 mg daily in the form of sublingual methylcobalamin tablets

Hormonal therapy with bioidentical hormones may also be considered, especially in women. Numerous studies have shown that hormone levels that approximate late pregnancy can reduce the severity of MS, although there is controversy surrounding this idea, and studies have shown a rebound effect in MS symptoms after pregnancy. Before bioidentical hormonal therapy is initiated, a complete Female Hormone Panel is recommended. For more information on this test, call 1-800-544-4440.

### **MULTIPLE SCLEROSIS SAFETY CAVEATS**

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

#### **Coenzyme Q10**

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

#### **DHEA**

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

#### **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

#### **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

#### **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

#### **NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric

mucosal barrier.

- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

### **Vitamin B12 (cyanocobalamin)**

- Do not take cyanocobalamin if you have Leber's optic atrophy.

### **Vitamin D**

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

### **Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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