



Analysis of research into the role of nutritional factors in the etiology of multiple sclerosis

Draft August 11, 2006
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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Currently, little is known about what causes this disease. Evidence that the incidence of MS is increased in blood relatives of people with MS suggests the role of genetic factors. However, epidemiological data indicating variations in MS prevalence across geographic regions as well as the incomplete concordance of MS between identical twins imply that an environmental component is also important in the etiology of MS.

Nutrition has been implicated as a possible etiological factor in MS. Like the prevalence of MS, diet can vary depending on ethnicity or location and may change upon migration to another country or environment. The finding of one or more dietary risk factors for MS would be a significant accomplishment in understanding how the disease develops, and could lead to measures useful for preventing or ameliorating the disease.

This Cure Map document (part of Phase II of the Nutrition track) reviews published research focusing on potential nutritional triggers of MS. The findings are organized according to the framework set out by the Phase I Nutrition document of the Cure Map:

- Nutrient properties
- Basis of nutritional diseases
- Nutrient vectors
- Pharmacokinetics and pharmacodynamics of nutrients
- Individual and group factors influencing nutritional disease

To prepare this review, we performed literature searches on "multiple sclerosis" together with key words and phrases from the Phase I document. We also examined the reference lists for the documents that were found to identify other related studies. Types of studies that were considered relevant ranged from ecological studies to case-control studies (both retrospective and prospective) to clinical trials of diets and dietary supplements. It should be noted that each of these types of studies have disadvantages as well as advantages. For example, ecologic studies may have difficulties controlling potential confounders, while case-control studies can suffer from selection bias as well as the fact that people with MS may change their diet in response to their disease (Lauer 1997). The ideal study, a detailed, high-frequency prospective analysis of the diet of people at risk of developing MS, has not been conducted; indeed, such a study would potentially have to be conducted from childhood since it is not known at what age MS begins to develop in any specific person.

Supporting material can be found in "MS Nutritional Studies," which is a database summarizing the details of the studies referred to in this document. A separate document, "Analysis of specific nutritional factors in the development of MS," reviews and assesses the research conducted to date on the nutrients that have been most thoroughly studied for a role in MS. Each of these documents can be downloaded from the Accelerated Cure Project web site at www.acceleratedcure.org/curemap/docs.php.

Nutrient Properties

Although any type of nutrient could conceivably play a role in the development of MS, to date, vitamins, minerals, and lipids have received the most attention in the MS scientific literature. The evidence for these and other types of nutrients as risk factors for MS are briefly discussed here. More detailed information about several individual nutritional factors can be found in “Analysis of specific nutritional factors in the development of MS.”

Fat-soluble vitamins such as A, D, E, and K have specific roles in body functions such as myelin formation and immune system function; disruptions of these functions due to nutritional imbalances could possibly therefore increase the risk of MS. Of these four vitamins, the strongest evidence for a correlation with MS exists for vitamin D deficiency. Evidence that vitamin D deficiency may predispose a person to MS comes from a variety of sources: ecological studies that evaluate exposure to vitamin D sources like sunlight, fish, and supplements¹⁻³, studies reporting associations between lesion activity and low vitamin D levels or sunlight exposure^{4,5}, and studies of bone density and vitamin D levels¹. The results of vitamin D supplementation studies in ameliorating MS have been inconclusive, however^{6,7}.

A few studies have investigated vitamin A (retinol or carotenoid) levels or intake in MS and non-MS controls, but most reported no associations⁸⁻¹⁰. Evidence is mixed concerning the involvement of vitamin E in MS. Although some studies have reported lower levels of vitamin E in the serum or cerebrospinal fluid (CSF) of MS subjects compared with controls, others were not able to detect any significant differences^{8,11-13}. Furthermore, intake of vitamin E supplements has not been shown to protect against MS¹⁰, although it has been suggested that vitamin E therapy may be beneficial in inhibiting the disease course of people with MS with signs of significant oxidative stress¹³. Vitamin K has not yet been assessed for a possible role in MS.

Water-soluble vitamins are broadly distributed throughout the body and include vitamins B₁ (thiamin), B₂ (riboflavin), B₃ (niacin), B₅ (pantothenic acid), B₆ (pyridoxine), B₇ (biotin), B₉ (folic acid), B₁₂ (cobalamine), and C (ascorbic acid). Most of the B-complex vitamins have not yet been assessed with respect to MS, although some of them such as niacin, pyridoxine, and biotin are known to play a role in the nervous system and/or can result in neurological deficits if too much or too little is consumed. Thiamin and riboflavin have only been assessed in MS by one study using a 164-item food frequency questionnaire, which found a protective influence for each⁹.

The only B-complex vitamin that has been studied extensively for involvement in MS is cobalamine (B₁₂), a cofactor for myelin synthesis. Like MS, vitamin B₁₂ deficiency is characterized by demyelination and axonal degeneration, and causes symptoms such as weakness, paresthesia, and unsteady gait. Indeed, vitamin B₁₂ deficiency and MS can be difficult to differentiate because they can share a similar clinical disease presentation as well as similar MRI findings¹⁴. Therefore it is not unreasonable to conjecture that lack of vitamin B₁₂ might be a trigger of MS. However, evidence is mixed concerning whether vitamin B₁₂ deficiency does increase the risk of MS. Some studies have reported an association between MS and low vitamin B₁₂ levels while other show no correlation¹⁵⁻²². Studies of serum methylmalonic acid (MMA) and homocysteine (HCY) concentrations, which tend to indicate severe intracellular B₁₂ deficiency, also present inconclusive evidence^{17,19}. Trials of high doses of vitamin B₁₂ in MS have shown only minor benefits¹⁸.

Evidence regarding the effect of dietary vitamin C intake on the risk of MS is limited. One case-control study using a food frequency questionnaire mentioned a negative association between higher intake of vitamin C and the risk of MS⁹. However, a prospective study of two large cohorts of women reported that higher intake of vitamin C was unrelated to reduced risk of MS, even after long-term intake lasting more than 10 years¹⁰. The effects of vitamin C supplementation in existing MS has only been assessed in a small, uncontrolled study in which several nutrients were administered simultaneously²³.

Minerals, due to their size and electrochemical properties, tend to play very specific roles in the functioning of the body. Their functions can be closely related; in fact, some minerals can substitute for another when there is a deficiency. Imbalances can also occur between two or more minerals and may appear as a deficiency. Perhaps for these reasons, MS studies evaluating the involvement of individual minerals are uncommon. Instead, most studies assess the presence of a variety of minerals at once. For example:

- A multi-trace element analysis of scalp-hair samples mentions significantly lower concentrations of

copper, iodine, manganese, sulfur, and vanadium and a significantly higher selenium level in scalp-hair samples of MS subjects. No difference was observed for several other elements including aluminum, calcium, chlorine, and zinc²⁴.

- An investigation of daily urinary excretions of trace elements in MS subjects revealed no significant difference in metals (lead, nickel, silver, copper, iron, molybdenum, and zinc) between MS cases and controls. Since no significant differences were noted, the authors conclude that it is unlikely that a metabolic imbalance of trace metal or environmental metal toxicity causes MS²⁵. This study, however, was very small, consisting of only 12 MS subjects and 12 controls.
- A study of an MS cluster focus (area of increased MS prevalence) concluded that an environment predisposing to MS may consist of soil low in copper, iron, and/or vanadium and high in lead, nickel, and/or zinc, as well as water high in chloride, chromium, molybdenum, nitrate, and/or zinc and low in selenium and/or sulfate^{26, 27}.
- **Macrominerals:** Most macrominerals, including sulfur, phosphorus, potassium, sodium, and chlorine remain generally unexplored as potential etiological factors for MS, with the exception of the studies mentioned above and a food frequency study that found a potential protective effect for potassium⁹.

Calcium and magnesium have each been evaluated in a few studies. The scalp-hair analysis referred to above found no difference in magnesium or calcium concentrations in samples from MS subjects and controls²⁴, and a study of serum and CSF reported no statistically significant difference in magnesium levels between MS and non-MS subjects²⁸. However, a food frequency study found a protective effect for calcium with respect to MS⁹, and a study of autopsy samples reported significantly lower magnesium content in visceral organs and central nervous system (CNS) tissues, particularly white matter and demyelinated plaques, in MS subjects compared with controls²⁹. A small, uncontrolled study of the effects of dietary supplementation with calcium, magnesium, and vitamin D reported a decreased relapse rate of MS⁶.

- **Trace minerals:** In comparison with macrominerals, trace minerals tend to have been investigated more extensively for a possible role in MS, with several having been analyzed using a variety of sample types. Iron, for instance, has been assessed not only in blood and urine (with no significant differences found in MS samples compared with controls) but also brain tissue, with one study finding evidence for iron deposits around demyelinated plaques³⁰ and another failing to find such deposits³¹. Zinc has been evaluated in studies of blood (plasma, serum, whole blood and erythrocytes), CSF, urine and scalp hair. Studies using blood products have reported mixed results, with some finding higher and others finding lower or normal zinc levels in MS subjects^{28, 32-36}. One study reporting higher zinc levels in MS subjects in whole blood noted that zinc increases in whole blood are also seen in other CNS diseases³⁷. Studies using other tissues have found no significant differences in zinc concentrations between cases and controls.

Results for copper are also mixed. Although most studies report only insignificant differences in blood, CSF, and urine copper levels between MS cases and controls^{11, 25, 28, 36, 37}, one study reported significantly elevated CSF copper levels in MS cases³⁸ and two other studies reported lower serum copper concentrations in MS cases^{28, 33}. Another study also detected significantly lower copper concentrations in the scalp hair of MS cases versus controls²⁴. In a similar fashion, studies of selenium and glutathione peroxidase (GSH-Px) activity have varied in their results and conclusions regarding this element's possible involvement in the etiology of MS^{11, 24, 36, 39-41}. In terms of intervention studies, one such effort reported increased GSH-Px activity following supplementation with selenium, vitamin C, and vitamin E, but clinical effects were not reported in this study⁴². Another study which noted signs of significant oxidative stress (in the form of reduced erythrocyte GSH-Px) in MS subjects suggested antioxidant supplementation with selenium to compensate but did not actually test out the recommendation¹³.

A few other trace minerals, including molybdenum, nickel, chromium, iodine, and manganese, have been assessed in MS but only a limited fashion^{24-26, 38}.

- **Ultra-trace minerals:** Aside from arsenic, which was found in normal quantities in scalp hair samples of

MS subjects²⁴, and vanadium, which was explored in a study of soil in an MS cluster²⁶, ultra-trace minerals such as fluorine, silicon, boron, and lithium and germanium have not been assessed.

Carbohydrates are a favored energy source in humans. In the MS literature, they are generally described in terms of the foods in which they are found, such as the starch in gluten grains or the sugars in sweets.

Gluten is a mix of elastic proteins found in wheat, rye, barley, and other cereal grains. Gluten proteins can cause immune responses, and thus have been postulated to play a role in autoimmune diseases. As described below in the “Vectors” section, studies examining whether MS subjects consumed above-average amounts of cereal and bread have produced mixed results.

Although gluten-free diets have helped reduce symptoms of other autoimmune diseases, such as celiac disease⁴³, only one pilot study has been reported in MS⁴⁴, and gluten antibodies do not appear to be frequently present in MS subjects⁴⁵. Immunologic cross-reactivity and molecular similarities between gluten and self-antigens have been reported in studies of celiac disease^{46, 47}; no such relationships have been reported in MS, although one study of autism subjects detected antibody cross-reactivity between a gluten peptide (gliadin) and cerebellar antigens⁴⁸.

Aside from food frequency studies that inquired about consumption of sweets such as chocolate, no effort has been made to specifically investigate a potential etiological role in MS for sugars. Likewise, the role of glycogen in MS has not been discussed.

Lipids serve as an energy storage medium, provide structure to cells, and can be converted into other types of chemicals such as hormones and vitamins. Myelin is composed primarily of lipids, and these nutrients, particularly saturated and polyunsaturated fatty acids (PUFAs), factor significantly in the MS medical literature.

- **Essential fatty acids (EFAs)** are polyunsaturated fatty acids that must be obtained from the diet since they are not synthesized in the body. The two EFAs are omega-6 (linoleic acid), and omega-3 (linolenic acid). EFAs are important to the nervous, immune, cardiovascular, and reproductive systems. EFAs also produce prostaglandins, which regulate inflammation and body functions such as heart rate and blood clotting.

A few studies have reported lower levels of omega-3 fatty acids in various tissues of people with MS compared with controls⁴⁹⁻⁵¹ although one failed to find any differences in red blood cells⁵². Other studies have linked lower fish intake with increased MS risk, which also suggests that omega-3 may protect against MS since fish oil is high in omega-3 fatty acids, although again not all studies are consistent⁵³⁻⁵⁶. Omega-3 supplementation trials have not shown sufficient clinical benefit to add weight to the hypothesis that omega-3 deficiency is involved in MS etiology^{6, 23, 57, 58}.

Omega-6 fatty acid levels, particularly linoleic acid levels, have been observed to be significantly lower in the blood and brain of MS subjects compared with both normal or neurological controls. Decreased concentrations of linoleic acid have also been reported in MS subjects in serum lipids^{59, 60}, total plasma⁶¹, and CSF⁶². Lower linoleate concentrations in serum lipids could be due to an altered rate of linoleic acid entry into or removal from the blood⁵⁹ or a defective metabolic pathway that is necessary in the absence of large amounts of linoleate⁶⁰. Analysis of the absorption of safflower and sunflower oil in MS cases indicated that lowered fatty acid levels in the CSF and serum of MS subjects are not due to dysfunctional intestinal absorption^{60, 62}.

Linoleate supplementation, which has been studied extensively, has yielded mixed results. Several studies have found increased linoleic acid levels in both MS cases and controls after supplementation^{60, 63-65}, but various double-blind, controlled trials have reported different effects of supplementation on relapses and disability associated with MS or have detected no therapeutic effect at all^{63, 65-67}. In general, larger clinical studies are needed to assess the effects of omega-6 dietary intervention.

- **Saturated fats** have been studied fairly extensively in the MS literature, with mixed results. Several epidemiological studies have suggested a positive association between MS and consumption of

saturated and animal fat (meat, milk, butter, and eggs)^{9, 53-55, 68-73}. In contrast with epidemiological studies, however, many population-based case-control studies have failed to confirm the relationship between fat intake and MS risk. Some studies have observed that MS subjects and controls did not differ significantly in frequency of fat intake before the onset of MS, suggesting that fat consumption is not associated with increased MS risk^{56, 74, 75}. A few studies have assessed the clinical effect of a reduction in dietary saturated fat (combined with an increase in polyunsaturated fat intake); each reported some degree of clinical benefit but it should be noted that these trials were all uncontrolled^{23, 64, 76}.

- Trans fatty acids have been addressed in only one study on the role of milk in MS, which discusses the trans fatty acid vaccenic and its potential to increase MS susceptibility. Trans fatty acids may alter membrane structure, accelerating demyelination and allowing easier access through the blood brain barrier, though evidence is mixed about whether or not vaccenic acid can enter the brain⁵⁴.
- Monounsaturated fats come from many of the same sources as polyunsaturated fats, such as olive oil, canola oil, and nuts. Oleic acid, a nonessential fatty acid with one double bond, is the most common monounsaturated fat found in the diet. Oleic acid supplementation of MS subjects has often been used as a placebo control in experiments involving linoleic acid, an omega-6 EFA^{57, 63, 65}, but has not been specifically discussed as a factor that may affect the risk of MS.
- Phospholipids have not been extensively assessed. An evaluation of a low-fat diet treatment also analyzed other lipids, noting no significant differences in phospholipid content of MS subjects and controls⁷⁷.
- Triglycerides, which exist in butterfat, animal lard, and oils, have also not been extensively assessed. A study of nonenzymatic antioxidants of the blood found a significantly lower ratio of vitamin E to cholesterol plus triglyceride during exacerbation, but reported no significant differences in plasma triglyceride levels between MS subjects and controls⁸.
- Steroids in the form of corticosteroids are often used to treat relapses in MS patients. The influence on corticosteroids on the risk of developing MS has not yet been assessed. However, their use may affect the concentrations of other nutritional elements in the body which may affect the results of nutritional studies. For example, in a small study of trace element status in MS subjects with and without corticosteroid treatment, elevated red blood cell (RBC) zinc-copper ratios were found in MS subjects compared with controls; ratios were particularly enhanced in those subjects receiving steroid treatment. These results suggest that a copper and zinc imbalance may either cause or result from MS and can be affected by corticosteroid therapy³⁶.

Another type of steroid that has been studied with respect to MS is cholesterol. An evaluation of a low-fat diet treatment noted no significant differences in the cholesterol content of MS subjects compared with controls⁷⁷; similar findings were reported in a study examining anti-oxidant levels in MS⁸.

Amino acids

Individual amino acids (lysine, glycine, tyrosine, etc.) as derived from food have not been discussed in the MS literature as potential factors influencing the risk of MS.

Peripheral chemicals (phytochemicals)

Of the various types of peripheral chemicals, only phytoestrogens, carotenoids, and flavonoids have been mentioned briefly in the MS literature. Catechins, lactoferrin, isothiocyanates, diallylsulfides, and monoterpenes have not been assessed.

Phytoestrogens. According to one review, because women with MS tend to have less frequent relapses during pregnancy and more frequent relapses in the months after delivery, estrogen is thought to slow disease progression⁷⁸. The same review mentions a recent study observing an ameliorating effect of quercetin, a flavonoid phytoestrogen, on the progression of the animal model experimental autoimmune encephalomyelitis (EAE) as well.

Carotenoids. Provitamin A carotenoids can be converted into vitamin A and function as antioxidants. Two

small studies have analyzed plasma or serum levels of beta-carotene in MS subjects and healthy controls; one found decreased levels in MS subjects (along with decreased levels of other antioxidants)⁷⁹ while the other found no significant differences⁸⁰. A prospective study using a food frequency survey indicated that higher intake of dietary carotenoids was unrelated to a reduced risk of MS¹⁰. Therefore, at this time, evidence does not suggest that carotenoids play a significant role in the etiology of MS.

Flavonoids. Experiments have shown that flavonoids can protect axons and oligodendrocytes from oxidative damage and phagocytosis⁸¹⁻⁸³; however, no connection between flavonoid deficiency and MS has been demonstrated.

Water

The role of water as a result of its function in the body has not been discussed in the MS literature. Water as a nutrient vector, however, has been mentioned briefly. Please refer to the "Drinking Water" section of this document for further information.

Basis of Nutritional Disease

An appropriately balanced diet is necessary to avoid deficiency, toxicity, imbalance, and misuse of nutritional factors and to maintain good health. At the extremes of the nutritional spectrum, inadequate amounts of a nutrient in the body signify a state of deficiency, while excessive amounts characterize toxicity; imbalance combines features of both. Misuse describes the improper buildup of nutrients in the body due to altered biochemical mechanisms. Each of these states could potentially lead to disease, either directly or indirectly.

MS does not provide any overt clues about which, if any, of these nutritional states may be involved in its etiology. For example, no reports have been made of MS prevalence rates consistently rising following sudden shortages of particular nutrients in particular populations, or of MS frequency being elevated in people following certain extreme diets. Therefore all possible states must be considered. The MS literature describes the use of several different types of experiments to determine whether subjects with MS have abnormal exposures to or concentrations of certain nutrients. Common experimental techniques include food frequency questionnaires, ecological studies of food usage in different geographical regions, and evaluation of serum and CSF samples for nutrient levels. Studies that alter the diets of people with MS to determine whether any beneficial effect can be detected can also provide information about nutritional contributions to MS.

Following are short summaries of the evidence generated for each of the four nutritional disease states (deficiency, toxicity, imbalance, misuse) as a risk factor for MS. For more information on the findings for individual nutrients mentioned in this section, please refer to the document, "Analysis of specific nutritional factors in the development of MS."

Deficiency: A variety of nutritional deficiencies have been investigated for a possible role in MS, including deficiencies of vitamin D, vitamin E, vitamin B₁₂, calcium, manganese, and essential fatty acids. At this point, although evidence has been produced linking MS with certain deficiencies, findings are often mixed or based on limited results. Furthermore, remaining to be explained is how any of these deficits might contribute to the pathological processes that initiate MS.

- Vitamin D. As noted above, several types of studies (including ecological studies and prospective intake surveys) have reported an association between lower levels of vitamin D and the development of MS. These deficiencies may come about through dietary practices or lack of exposure to sunlight, and may affect the immune system in a way that increases the risk of MS. More study is needed to confirm and explain these findings.
- Vitamin B₁₂. Vitamin B₁₂ deficiency and MS share many neurological symptoms, including weakness and fatigue. It is reasonable to suggest that vitamin B₁₂ deficiency could increase the risk of MS, and in fact many (although not all) studies of vitamin B₁₂ levels in serum and CSF show a decrease in people with MS compared with controls.
- Vitamin E. Severe vitamin E deficiency can also damage nerves and cause symptoms similar to those seen in MS, such as impaired sensations, lack of coordination, and muscle weakness. As with vitamin B₁₂, evidence from case-control and prospective cohort studies is mixed regarding whether MS is

associated with lower levels of vitamin E.

- Calcium. There is evidence, although limited and inconclusive, that lower levels of calcium are associated with MS. Calcium depletion may also help account for the bone loss and osteoporosis often observed in MS subjects.
- Zinc. A few studies have reported zinc deficiency in the plasma of MS subjects, although many other studies of blood products and other tissues found no evidence of deficiency. Possible explanations for low zinc levels in MS include malabsorption³³, disease activity³⁷, and chronic inflammation or abnormal zinc regulation³⁵.
- Manganese. A few studies of various tissues (such as CSF and scalp hair) have reported that manganese levels are decreased in MS cases, but, as is the case with most trace elements, not enough evidence exists to make a definite conclusion.
- Essential fatty acids. Several studies, including serum and CSF measurements and food intake studies, suggest that MS subjects are deficient in both omega-3 and omega-6 fatty acids. Omega-6 fatty acid levels have been found to be significantly lower in the brain and blood of MS subjects and can be corrected by sunflower oil or evening primrose oil supplementation. Since the Western diet already consists of much more omega-6 than omega-3, however, increasing n-3 fatty acid intake while maintaining n-6 intake may provide the most appropriate balance of the two EFAs (see "Imbalance" below).

Toxicity: Of all the nutrients studied in MS, saturated fat is the only one for which an *increase* in intake has been repeatedly linked with MS. Since the myelin sheath is composed mainly of lipids, it has been proposed that excess saturated fat intake could alter myelin sheath stability. Low-fat treatments, such as the Swank diet, have been devised to correct the toxicity. Positive results in terms of clinical outcomes of people with MS have been reported from studies of these diets, but it should be noted that these studies were not controlled and randomized^{76, 84}.

Imbalance: MS risk could potentially be influenced by a state of imbalance between a number of nutritional factors, including saturated and polyunsaturated fats, omega-6 and omega-3 essential fatty acids, and zinc and copper:

- Saturated and unsaturated fats. A study of essential fatty acids in the serum and CSF suggests that MS subjects have an imbalance between saturated and unsaturated fatty acids, which may be pronounced during acute MS exacerbation⁶². A diet with excess saturated fat could produce a relative deficiency of EFAs, creating a lipid imbalance that could affect cell fluidity, myelination, and synthesis of immunoregulatory compounds⁷³. Alternatively, instead of just creating a deficiency in EFAs, saturated fats may actually antagonize the functions of eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), two omega-3 unsaturated fatty acids, which may lead to an inflammatory leukotriene response^{85, 86}.
- Omega-3 and omega-6 fatty acids. In the Western diet, the ratio of omega-6 to omega-3 fatty acid intake is close to 20:1. MS rates tend to be higher in regions where Western diet practices are observed, suggesting that an omega-6:omega-3 imbalance could play a role in MS. According to one review, omega-3 EFAs from fish oil are immunosuppressing nutrients that help prevent EAE disease progression, while large amounts of omega-6 EFAs inhibit the effects of omega-3 EFAs⁸⁷. Therefore, deficiencies in omega-3 fatty acids with respect to omega-6 EFAs could alter immune regulation in a way that leads to MS.
- Zinc and copper. A possible zinc-copper imbalance may be a cause or consequence of MS. A study with a small sample size observed decreased copper content and elevated zinc-copper ratio in the red blood cells of MS subjects compared with controls³⁶.

Misuse (failure of the body to properly process, use, or excrete a nutrient, as is seen in phenylketonuria, for instance) has not been explicitly assessed in the MS literature.

Nutrient Vectors

Nutritional vectors are the means by which nutrients enter the body. In MS, the vectors that have been most

frequently assessed are food and sunlight. As stated in the previous section, no unusual disruptions in or overuses of a particular vector have been prominently associated with MS. However, vector preferences and availability do differ among populations and individuals; therefore any such differences that can be associated with MS may help reveal nutrients involved in the etiology of the disease.

Food is the major vector for nutrient entry into the body. Exposures to different types of food are primarily assessed by ecological studies of food consumption and case-control food frequency studies. Studies show that meat and other animal products, dairy, and fish oil have potentially significant roles in MS, while other foods such as fruits and vegetables and sweets appear to play a minor role, if any at all.

- Meat and other foods of animal origin. Many studies cite an association between MS and the intake of meats that are high in saturated fat as well as nutrients such as proteins and amino acids. Several epidemiological studies have suggested a positive association between MS and high saturated and animal fat consumption. For instance, one study of 22 countries for which data on MS prevalence and diet were available reported a significant, positive correlation between MS prevalence and animal fat intake⁶⁸. An epidemiologic study of nutrient intake and death rates revealed that mortality from MS was correlated with consumption of meat, milk, butter, and eggs⁶⁹. In an ecologic study, significant correlations were found between MS prevalence and fat intake, total meat intake, and pork consumption. Beef consumption, however, was not significantly correlated, even though beef and pork have the same fat composition⁷⁰.

In contrast with epidemiological studies, however, many population-based case-control studies fail to detect a relationship between fat intake and MS risk. These studies have observed that MS subjects and controls did not differ significantly in frequency of meat and fat intake before onset of MS, indicating that fat consumption is not associated with increased MS risk^{56, 74, 75}.

- Dairy. Evidence is also mixed regarding the influence of dairy product consumption on the risk of MS. While ecologic studies report a strong positive correlation between MS and dairy food consumption^{53-55, 69, 88, 89}, many case-control studies report no difference in intake between MS cases and controls^{74, 90-92}. However, a few case-control studies have found that greater dairy intake was associated with MS^{71, 72, 93}. Living on a farm has also been reported as a risk factor^{91, 93, 94}, especially in comparing the high incidence of MS in farming regions as opposed to coastal regions^{53, 68}. However, a number of confounding factors, such as socioeconomic status^{53, 68, 95}, an agricultural lifestyle⁹¹, or climate⁵⁵ may affect the validity of these conclusions.

Some speculations have been made about specific dairy products or components that could be responsible for an increase in MS risk. Fresh cow milk intake is more closely correlated with MS than cream, butter, and cheese, suggesting the presence of a factor in cow milk, such as an oxidative product of dairy called butyrate, that may trigger the development of MS^{54, 89, 92}. In addition, fresh unpasteurized milk could be a potential risk factor for MS by acting as a vector for bacterial or viral agents^{55, 92}. The high concentration of saturated fatty acids in many dairy products could also help explain the higher risk of MS⁷¹. Calcium in milk has also been discussed as a potential factor in MS etiology⁹⁴.

- Breast milk and infant formula. Breast feeding of infants has been proposed to reduce their future risk of MS, either by providing essential nutrients such as unsaturated fatty acids found in breast milk, by affecting the immune system of the infant, or by reducing the intake of cows' milk or other substances that may increase susceptibility to MS. Two studies supporting this hypothesis found that MS subjects reported being breastfed as infants for shorter periods of time on average than controls^{96, 97}. However, previous studies found no association between formula or breast feeding and MS^{75, 98}. The impact of breast feeding on MS needs further study before any conclusions can be drawn.
- Fish/fish oil. Fish and fish oil intake is of particular interest in MS research because fish oil is high in omega-3 fatty acids. Some studies have reported lower rates of MS in regions where fish intake is high⁵³⁻⁵⁵, and differences in fish intake have been proposed as an explanation for lower MS rates in coastal vs. inland regions in certain countries such as Norway. However, an analysis of data from the Nurses' Health Study revealed no protective effect of consumption of omega-3 fatty acids from fish⁵⁶.

The clinical effects on MS of fish oil supplements have also been analyzed. Results suggest that such treatment may lead to reduced exacerbation rate^{6, 57, 58} and decreased disability^{6, 57, 58, 76, 85}. However, these studies tend to have limitations such as small numbers of participants or lack of a control arm.

- **Cereals and breads.** A few case-control studies of dietary practices have assessed intake of cereals and breads in MS and control subjects. Results have been contradictory, with one study concluding that high consumption of cereal-derived products correlated positively with MS⁷², another finding instead a protective effect of higher cereal and bread intake⁹ and a third finding no significant relationship between cereal/bread intake and risk of MS⁷¹.
- **Fruits/vegetables.** Usually, fruits and vegetables are mentioned only as one of a variety of factors assessed in food frequency studies. From the few studies that are available, there is a general consensus that frequency of fruit and vegetable consumption is not related to the risk of MS^{10, 74, 92}.
- **Sweets.** A few studies mention an association between consumption of sweets and risk of MS. One population-based study observed no significant differences in diet except slight differences in intake of sweets such as cake, cocoa, and chocolate⁷⁴. Similarly, one food frequency survey found an increased risk of MS, in females only, with consumption of sweets such as candy, jam, jelly, and chocolate⁹. Another similar case-control study observed a positive correlation between high incidence of MS and frequent consumption of coffee, tea, and cocoa⁷². One hypothesis states that an allergic reaction to cocoa products may cause MS⁹⁹.

Drinking water has not been discussed independently of other factors in any MS study. Rather, drinking water is usually mentioned as one of a number of environmental factors surveyed in questionnaires. Of a few case-control studies of exposure to various exogenous factors, two studies indicated that a higher percentage of MS subjects compared with controls drank from a piped water supply^{74, 91}. Two different studies, however, found no difference in source of water or drinking habits of MS subjects and controls^{75, 90}. In a study of a high-risk MS cluster, the water contained large amounts of chloride, chromium, molybdenum, nitrate, and zinc and only trace amounts of selenium and sulfate²⁷, suggesting the possible contribution of an environmental factor to MS.

Supplements are primarily used to treat or prevent the deficiency of a nutritional factor. In a prospective study of two large cohorts of women (Nurses' Health Study I and II), it was concluded that vitamin C, E, and multivitamin supplementation were unrelated to the risk of MS¹⁰. However, in a follow-up analysis, the same authors concluded that there was a 40 percent reduction in risk of MS among women who use supplemental vitamin D, typically in the form of multivitamins³. The authors noted that they faced limitations in separating the effects of vitamin D intake from other components of multivitamins (vitamin E, folic acid, zinc, B₁, B₂, B₆, B₁₂).

Air as a vector (e.g., of oxygen) has not been assessed in any study relating nutrition to MS.

Sunlight is the means by which ultraviolet radiation (UVR) is carried to the Earth's surface. Exposure of skin to sunlight catalyzes the production of vitamin D₃, the precursor of the stored and active forms of vitamin D. Lack of UVR may play a causal role in MS by creating a vitamin D deficiency, thus potentially accounting for the latitude gradient of MS incidence (increasing MS prevalence with increasing latitude)¹⁰⁰.

The relationship between sunlight exposure and MS has been investigated through regional comparisons of MS distribution rates to average annual hours of sunlight, case-control studies assessing amounts of outdoor activity and sunlight exposure, and studies of MS disease activity during different seasons. Most studies suggest a protective effect of sunlight exposure on MS, with high sun exposure corresponding with a reduced risk of MS^{2, 85, 101-103}. Some discrepancies do exist, however. One population-based epidemiologic study indicates that MS subjects actually spent more time outdoors in the summer and did not tend to have occupations with less outdoor exposure, thus contradicting the hypothesis of the protective effect of sunlight⁷⁴.

Pharmacokinetics describes what the body does to a nutrient, that is, how the nutrient is processed. In general, how the pharmacokinetics of nutrients relate to MS has not been widely assessed in the scientific literature.

Digestion

Although individual vectors and properties have been addressed in great detail, the organs necessary for digestion and the processes by which nutrient vectors such as food are broken down to vitamins and minerals are not generally covered.

Absorption – organs

The small intestine, which includes the duodenum, jejunum, and ileum, is responsible for absorption. Defects in intestinal absorption could potentially alter nutrient concentrations in MS subjects.

- The duodenum is responsible for fatty acid absorption. It has been suggested that lower linoleate concentrations in serum lipids could be due to an altered rate of linoleic acid entry into or removal from the blood⁵⁹ or a defective metabolic pathway⁶⁰. However, studies of absorption of safflower and sunflower oil in MS cases have indicated that lowered fatty acid levels in the CSF and serum of MS subjects are not due to dysfunctional intestinal absorption^{60, 62}.
- Hypotheses concerning MS and the absorption of zinc by the jejunum have been conflicting. While malabsorption has been cited as a possible explanation for low serum zinc levels³³, other studies of blood zinc levels suggest that altered zinc levels are probably not the result of zinc malabsorption or nutritional abnormalities^{35, 104} but rather reflect chronic inflammatory activity or abnormalities in control mechanisms³⁵. Biopsy studies of the jejunum in MS subjects also provide mixed results, with some reporting structural and biochemical abnormalities¹⁰⁵ and others reporting none^{106, 107}.
- Malabsorption of vitamin B₁₂ by the ileum is one cause of B₁₂ deficiency, which has been detected in some MS subjects¹⁴. However, no evidence exists showing that people with MS have any dysfunction in this organ.

Malabsorption of the various nutrients absorbed by the colon has not been assessed.

Absorption – processes

Studies of MS and nutrition have not gone into detail about the specific processes, including active transport, passive diffusion, facilitated diffusion, and phagocytosis, through which absorption can occur.

Distribution

The mechanisms by which most nutrients are distributed throughout the body have not yet been fully assessed for potential involvement in MS. However, a few studies have investigated the role of protein carriers which transport certain minerals and vitamins, and which could therefore influence the concentrations of these nutrients in the tissues of people with MS. For example, copper is transported by ceruloplasmin, an enzyme that also plays a role in modulating lipid peroxidation. A small study of trace element status, however, found no deficiency in plasma ceruloplasmin in MS subjects³⁶.

An alteration in the primary protein carriers for zinc in the blood could indicate zinc deficiency in people with MS. Various studies have found abnormalities in MS subjects in terms of zinc or zinc carrier (e.g., albumin, alpha-2 macroglobulin) concentrations although discrepancies exist within these findings^{32, 33, 35, 104}.

One study found elevated levels of a vitamin B₁₂ transport protein called R-binder in MS subjects compared with normal and other neurological disease (OND) controls, but the significance of this finding was not known²².

Transformations

Though individual nutrient vectors and properties have been studied extensively, the steps by which these nonspecific nutritional factors are converted into usable form for highly specific functions in the body have not been assessed in terms of MS.

Storage

In general, improper storage of nutrients has not been extensively studied in connection with MS. Some studies have detected increased iron deposition in MS brain tissue^{108, 109} which may contribute to tissue

damage. However, it is unclear how these deposits are formed (one hypothesis is that deposition is mediated by upregulation of heme oxygenase-1 in astroglia¹¹⁰). Another small study that observed significantly elevated copper levels in the CSF of MS subjects postulated that MS causes changes in the brain that alter metal uptake, distribution, and storage that are then detectable in the CSF³⁸.

Excretion

Analysis of excretions can help investigators assess the intake as well as the appropriate processing of certain nutritional factors. For example, an investigation of daily urinary excretions of trace elements in MS subjects revealed no significant difference in metals (Pb, Ni, Ag, Cu, Fe, Mb, Zn) between MS cases and controls²⁵. It has not yet been suggested, however, that excretion abnormalities are involved in the development of MS.

Pharmacodynamics describes the effect that a nutrient has on the body. Deficiency, toxicity, imbalance, and misuse of nutritional factors can have different effects that could be involved in the etiology of MS. The mechanisms by which various nutrients could play a role in MS are still under investigation. Proposed mechanisms of nutrient actions important in MS include regulation of the immune response, myelination/demyelination, and function of the blood brain barrier (BBB).

Regulation/stimulation of the immune response

- Vitamin D and UVR. Ultraviolet radiation appears to have immunosuppressive effects on T helper 1 (Th1) cell immune responses^{2, 111} which may modulate autoimmune attacks in MS. This effect may be mediated by the impairment of antigen-presenting cells, the induction of regulatory T cell activity, and/or the suppression of melatonin, which enhances the release of Th1 cytokines. Vitamin D, which is synthesized via UVR exposure as well as ingested through the diet, is also thought to inhibit Th1 activity and promote regulatory T cell function¹¹².
- Calcium. According to one study, calcium and 1,25-(OH)₂D₃ work together to regulate the immune system¹¹³, as has been demonstrated in experiments involving EAE, a T-helper cell-dependent autoimmune disease. Altered concentrations of either nutrient could affect immune system response.
- Trace metals. Dietary intake of metals such as zinc has been shown to influence the responsiveness of the immune system. Elevated levels of lead, nickel, and zinc in the soil of a high-risk MS cluster focus suggest that these trace elements may stimulate an immune response, perhaps by interacting with or altering the function of self-constituents²⁶.
- Polyunsaturated fats. PUFAs, especially n-3 fatty acids, produce various immunomodulatory and anti-inflammatory factors²³, which may affect the course of MS^{85, 86}. Modulatory effects of n-3 supplementation on immune function may involve altering the immune cell membrane and regulating metabolic pathways related to immune activation, such as cytokine or eicosanoid production¹¹⁴. An immunosuppressive function of PUFAs in existing MS is suggested by studies showing that linoleic acid supplementation may reduce the duration and severity of acute exacerbations^{63, 67}.
- Dairy/gluten products. The idea that food antigens could trigger an immune response leading to the development of MS has been investigated just a few times. One study showed an abnormal T cell response in MS subjects to cow milk proteins, similar to the response demonstrated by diabetes subjects¹¹⁵. However, no abnormal response to gluten proteins was found in another study⁴⁵.

Myelination/demyelination

- Vitamin B₁₂. Vitamin B₁₂ deficiency can lead to alterations in the lipid composition of myelin and therefore could play a role in the poor remyelination seen in MS. Defective synthesis of the myelin sheath may also trigger an autoimmune response which contributes to MS pathogenesis¹⁴.
- Zinc. Zinc is an essential part of carbonic anhydrase, which is a part of the myelin sheath. Decreased carbonic anhydrase activity as a result of zinc deficiency could change myelin metabolism and increase MS susceptibility^{32, 35}.
- Fatty acids. Since the myelin sheath is composed mainly of lipids, an imbalance in the composition of fatty acids available in the body could alter its function and stability⁷³. The composition of fatty acids and lipids in MS brain tissue (normal appearing white matter and plaques) has been analyzed in a few studies, with some finding alterations compared with control brain tissue and others finding no significant differences¹¹⁶⁻¹¹⁹.
- Calcium. It has been hypothesized that low milk intake during an adolescent growth spurt may lead to

inadequate levels of calcium with adverse effects on myelin lipid synthesis⁹⁴. Therefore, high childhood consumption of milk followed by a sudden decrease in adolescence could be related to MS incidence in young adulthood.

- **Antioxidants.** An excess of free radicals in the CNS can cause lipid peroxidation and induce protein and myelin sheath damage. Increased radical production with decreased antioxidant defense in the CNS may therefore help to promote the myelin damage seen in MS^{8, 120}.

Permeability of blood brain barrier

- **Saturated fat.** Several mechanisms have been proposed by which saturated fat could weaken the blood brain barrier, increasing the risk of MS. Swank's hypothesis (and the rationale for his low saturated fat diet) is that aggregation of blood cells following consumption of fats results in sludging of the blood, reduced oxygen availability in the brain, and increased vascular permeability in the central nervous system⁸⁴. Another theory is that dietary lipid imbalances can alter cell membrane function, leading to defects in the blood brain barrier⁵⁴.
- **Polyunsaturated fat.** Hutter has proposed that an excess of the omega-6 arachidonic acid and deficiency of omega-3 EPA and DHA leads to the overproduction of inflammatory leukotrienes which increase the permeability of the blood brain barrier⁸⁵.

Individual and Group Factors Influencing Nutritional Disease

Individual and group factors such as genetics, modernization, health status, geography, and cultural norms may alter a person's susceptibility to certain diseases. The following paragraphs discuss these factors and their possible relevance to a nutritional basis for MS.

Age

It has been postulated that development of MS is influenced by the occurrence of events at specific ages (such as adolescence). For instance, one study observed an association between age of migration and risk of MS in Asian immigrants moving to England, where the incidence of MS is considerably higher. Asian immigrants who entered England at an age younger than 15 had a higher risk of developing MS than those who entered after 15¹²¹, suggesting that the childhood to adolescent years before age 15 are critical to the risk of developing MS. Similar findings have been reported by other investigators (although it should be noted that not all migration studies find associations between migration age and MS risk¹²²).

Although it stands to reason that nutrition during childhood or adolescence may influence the risk of MS, only a few nutritional studies have actually investigated age-dependent differences between MS and non-MS cases. Two studies have found that plasma and serum levels of zinc and copper are lower in younger MS subjects compared with controls (but not significantly different in older subjects), but whether this relates to conditions at onset of MS is not known^{32, 33}. Another study found a strong inverse association between sun exposure in childhood and adolescence and risk of MS². It has been hypothesized that inadequate concentrations of nutrients such as calcium and phosphate during growth spurts (at the fetal stage and puberty) could potentially disturb myelin synthesis and cause MS^{94, 123, 124}. Other studies observed no notable differences in childhood diet⁷⁵ or vitamin E levels in different case/control age groups¹².

Genetics

A few studies have looked for possible associations between MS and genetic variants that affect the utilization of nutrients, in particular the metabolism and function of vitamin D. For example, several studies have assessed the vitamin D binding protein gene and the vitamin D receptor gene, with mixed results¹²⁵⁻¹³⁵. One study also examined the 25(OH)D2 1alpha-hydroxylase gene but found no evidence for linkage or association with MS¹²⁸. More information on genetic research in MS can be found in Phase 2 of the Genetics track of the Cure Map.

Modernization

The documented prevalence of MS has increased greatly since its original identification in 1868. Undoubtedly this is at least partly due to increased awareness of the disease and better diagnostic techniques, but some have wondered whether changes occurring in modern society, including increases in standards of living, may

also have increased the risk of MS.

- Socioeconomic status. Not all studies agree that socioeconomic status is related to MS^{54, 74, 91}, but studies that do report a correlation often suggest that higher socioeconomic status is associated with higher risk of MS^{55, 103, 124}. Greater affluence allows for better nutrition with higher meat consumption, which could potentially increase the risk of MS through intake of nutrients such as saturated fats⁵⁵. (Conversely, it has been suggested that the association between high animal fat intake and MS could merely reflect the relationship between MS risk and high socioeconomic level. However, this has been deemed unlikely since total calories and total protein have not been similarly associated with MS risk, as would be expected if a factor directly related to socioeconomic class was the causal agent⁶⁸.)

As a counterpoint to the supposition that high socioeconomic status is associated with MS, an investigation of MS incidence in New Zealand found instead a significantly higher proportion of MS subjects who had lived in rural areas before age 21 and probably came from lower socioeconomic backgrounds⁹⁴. Though contradictory to trends in the US, these results were consistent with the childhood milk intake patterns in New Zealand, where fresh milk is cheapest and most available to those of lower socioeconomic backgrounds.

- Food processing. It has been suggested that milk processing may destroy a factor that is related to the clinical appearance of MS and is present in unpasteurized cow's milk, since fresh cow milk intake has been more closely correlated with MS in certain studies than cream, butter, and cheese^{89, 92}. A proposed factor is butyrate, an oxidative product of dairy products⁸⁹.
- Fortification. Fortification of foods with minerals and vitamins has not been assessed for a possible effect on the risk of MS.

Health status

Intake and processing of nutrients can be greatly altered by a person's health status, and can therefore lead to further changes in health.

- Trauma/illness/addiction. Although trauma, illnesses, and addiction have been studied as possible risk factors for MS, with varying results, discussions of their involvement have not included their effects on nutritional health.
- Fitness. It has been reported that obesity occurs more frequently among MS cases due to immobility and an inactive lifestyle following diagnosis^{124, 136}. However, whether fitness level influences risk of developing MS in the first place has yet to be assessed.
- Occupation. Occupation can influence a person's health in a number of ways, for instance by increasing or limiting his or her exposure to certain nutritional factors. Living on a farm has been reported as a risk factor⁹⁴, especially in comparing the high incidence of MS in farming regions as opposed to coastal regions⁵³, although not all studies have found rural residence to increase the risk of MS⁹¹. Other occupations have been studied with respect to risk of MS, including metal processors, electricians, health service workers, and so on¹³⁷, but typically from a toxic agent exposure rather than a nutritional point of view.

Sunlight exposure is another nutritional factor that may affect the risk of MS and may be affected by choice of occupation. Many studies postulate a protective effect of sunlight, suggesting that occupations that offer greater exposure to sunlight decrease the risk of MS. For example, one such case-control study found a negative association between mortality from MS and residential and occupational exposure to sunlight¹⁰³. However, not all studies have found that MS subjects tended to have occupations with less outdoor exposure⁷⁴.

Geography

The availability of foods and nutrients is shaped by the environment in which a person lives; it is possible that geographic patterns of MS prevalence are at least somewhat influenced by nutritional factors.

- Flora and fauna. Differences in disease prevalence among geographic regions are sometimes due to

differences in the plants and animals available there. The reported associations between MS and coastal or rural environments which may be due to food intake have already been mentioned above. A review of ecological data by Lauer¹³⁸ also found correlations in several countries between MS and the cultivation of oats (but not wheat).

- **Geology.** Only a few attempts have been made to relate MS prevalence to the minerals present in soil. One example is the previously-mentioned study that characterized the soil and water contents in a region with high MS prevalence^{26, 27}.
- **Climate.** Most studies that mention climate indicate that latitudes closer to the poles, colder temperatures, and/or a lower amount of sunlight received are associated with a higher incidence of MS^{54, 55, 101}, although one study could not find an independent effect on MS risk apart from latitude for solar radiation, temperature or other climatic factors¹⁰². One hypothesis suggests that cold stress increases energy consumption and thus the need for fat and protein, leading to biochemical imbalances that may lead to MS¹²³.

Cultural practices

Cultural practices affecting nutrition that may affect the risk of MS have not been addressed extensively. However, the consumption of a local dish in the Orkney and Shetland Islands of Scotland, a region that maintains the highest MS rates ever reported, was associated with MS. The dish, called potted head or pig's brain, was the only one of six unusual food items that had any association with MS. The six food items included: potted head, raw fish, sea bird's eggs, undercooked meat, unpasteurized milk, and raw eggs⁹¹. Other local specialties have occasionally been associated with an increased risk of MS (e.g., horse meat in an Italian case-control study⁷²), but to date no strong influence of cultural dietary practices on MS prevalence has been documented.

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