The Critical Need for Dietary Research into the Cause and Progression of Multiple Sclerosis

Ashton F. Embry

Preface - This essay was submitted in January, 2000 to the Institute of Medicine (IOM) Committee on Multiple Sclerosis: Current Status and Strategies for the Future which was commissioned by the National Multiple Sclerosis Society (NMSS). The purpose of the essay was to convince the Committee to include a recommendation for research into the likely role that diet plays in MS onset and progression.

Introduction - I am pleased that the IOM committee is taking such a wide-ranging look at the current status of research into MS and strategies for future research efforts. I would note the committee has an impressive line-up of experts although I think that the committee would have been enhanced by at least one member from outside the medical field (eg an expert on chaos theory). Also there is no one from the client side of the fence, the inclusion of which might have also provided some unique perspectives. I suppose the committee can consider this input as being both from a scientist completely outside of medicine and also from a client.

I have been a geological research scientist for over thirty years and have worked mainly on large, multi-factoral problems such as the origin of the Arctic Ocean and the occurrence and causes of global base level changes. In 1995 my oldest child was diagnosed with MS and I have spent a great deal of time since then reading the extensive MS literature with the goal of identifying plausible causal factors of MS. In geology we accept the fact we can never know anything with absolute certainty and we concentrate on the simplest solution(s) which fit all available data. I have applied this same strategy to the epidemiological and pathogenesis database for MS. I would note that I have nothing to gain and all to lose from subjectively favouring one causal factor over another.

MS Cause - I would hope that the committee would unanimously agree that both genetic and environmental factors play significant roles in MS. My main interest is in the identification of the environmental factors and I believe this is a very important area for future research. Given the current data base for MS, I have concluded that the simplest (best) explanation for MS is that CNS autoaggressive T cells are activated in the periphery by foreign antigens and that these effector cells then cross the BBB and precipitate an autoimmune attack against one or more autoantigens associated with myelin. I note that this is not the only plausible cause for MS, just the one that best fits the data. Furthermore it is the one which is seemingly favoured by most researchers at this time.

This leaves important questions of what are the sources of the foreign antigens, how do they activate the autoaggressive T cells, and when does this happen. Again the simplest answers to these questions, given all the constraints of the data, are 1) sources of foreign antigens are both infectious agents and food, 2) activation of both naïve and memory Th cells is mainly by cross reactions induced by molecular mimicry between foreign and self antigens, and 3) such activation happens throughout the course of the disease in a chaotic fashion. I stress that all of these answers are not proven or either widely accepted, they just seem to me to be the best ones if all the data are honoured. I expect most members of the IOM committee would agree somewhat with this analysis with the notable exception of my inclusion of food being a source of foreign antigens which can result in the activation of CNS autoaggressive T cells. The main reason for this submission to the IOM committee is to expand on this concept and to argue for the need for research which determines whether or not food-derived antigens play a substantial role in MS onset and progression.

Food-derived Antigens - As stated earlier, I think most of the IOM committee, and indeed most MS researchers, would agree that foreign antigens play a major role in MS. So the question at hand is whether or not it is plausible that food-derived antigens are part of the foreign antigen load which drives MS. My

arguments for why food antigens quite possibly play a role in MS are below. Once one accepts that it is plausible (ie there is a reasonable chance) that food antigens contribute to MS progression, then there can be no doubt that research is necessary to decide the issue beyond a reasonable doubt. Furthermore, given the lack of industrial incentives for doing such research (no significant financial reward), only charitable and governmental organizations like NMSS and NIH can provide the necessary promotion and funding for such research.

Clearly, if it is found that food antigens do indeed play a role in MS onset and progression, then that will revolutionize MS research and treatment. How many other proposed research topics have that potential! So what is the circumstantial evidence that indicates that food antigens may be a significant factor in MS?

First of all, from a big picture view, it is reasonable to expect that food antigens may play a role in a disease like MS which can be lumped with a large number of chronic diseases in which both genetic and environmental factors play major roles. Eaton and Konner (1985) published a very important paper in NEJM which introduced the concept of Paleolithic nutrition. Simply stated, it argues that foods introduced into the human diet by the agricultural revolution (~6000-8000 years ago for northern Europeans) can potentially cause biochemical failures which lead to chronic illnesses in genetically susceptible people because humans have not had time to genetically adapt to such foods. Thus in a given population there will be a given percentage of people who are genetically incompatible with one or more of the newly introduced foods. These "new" foods include dairy products, grains, legumes and yeast as well as large increases in the consumption of sugar, salt and saturated fat. The pre-agricultural diet (Paleolithic diet) consisted of lean wild meat (low fat, low % of saturates), fruits and vegetables. There can be no doubt that the newly introduced foods have contribute substantially to other genetic-environmental (chronic) diseases such as heart disease, hypertension, stroke, type 2 diabetes and various forms of cancer. The question is do these new foods also contribute to autoimmune diseases including MS. The evidence which indicates that these foods do indeed play a role in autoimmune disease include:

1. The geographic variations in the prevalence of autoimmune diseases tend to match variations in food supply with higher prevalence occurring in areas where the new foods dominate the diets (temperate climates). For example it was shown that the correlation between milk consumption and MS prevalence was .84 (Malosse et al, 1992). Even more impressive was the almost one for one correlation between type 1 diabetes prevalence and consumption of a specific type of beta casein (.98!) (Elliott et al, 1999).
2. Animal experiments show that foods such as milk, wheat and soy can precipitate IDDM and RA in mice, rats and rabbits (Coombs and Oldham, 1981; Elliott et al,1984; Welsh et al, 1985; Scott, 1996). Little has been done in this regard for MS although I was recently in contact with Dr John Elliott of the University of Alberta who told me that his recent experimental work has demonstrated that NOD mice fed an elemental diet were resistant to MOG-induced EAE but lost that resistance when milk protein was added to the diet (J Elliott, pers. comm., 1999).
3. People with autoimmune diseases have T-cells and antibodies which cross react with both self proteins and food proteins (Martin et al, 1991; Perez-Maceda et al, 1991; Cheung et al, 1994; Ostenstad et al, 1995).
4. Molecular studies of proteins from wheat, milk, yeast and legumes show that they can have very similar molecular structures as self proteins and that peptides derived from food proteins activate autoreactive T-cells derived from people with autoimmune disease (Singh et al, 1989; Ostenstad et al, 1995; Cavello et al, 1996; Honeyman et al, 1998).
5. Clinical trials with people with RA and Crohn's disease, both organ-specific, cell-mediated autoimmune diseases with numerous immunological similarities to MS, show that avoidance of proteins from wheat, dairy and legumes results in major symptom improvement (Panush et al, 1986; Darlington and Ramsey, 1992; Riordan et al,1993; Haugen et al, 1994; Beattie and Walker-Smith, 1994; Husby et al, 1995; Kavanaghi et al, 1995; Fukuda et al, 1995; Zoli et al, 1997).

6. Gluten proteins from a variety of grains are the primary cause of two autoimmune diseases, celiac disease and dermatitis herpetiformis (Marsh, 1992; Bodvarsson et al, 1993). Also of note is that persons with celiac disease are much more susceptible to other autoimmune diseases including RA, IDDM, autoimmune thyroid disease, Addison's disease and alopecia areata (Lepore et al, 1996; Kaukinen et al, 1999).

To me, when all this epidemiological, experimental, clinical and theoretical evidence is considered as a whole, it is very reasonable to postulate that food proteins, especially those recently introduced into the human diet, may well play a role in a variety of autoimmune diseases including MS.

Infectious Agent-Diet Model for MS - Given this, it is still necessary to provide a theoretically plausible pathogenesis for MS which involves food proteins and there should be no major contradictions with the available epidemiological data base. Below is a simple hypothesis for MS pathogenesis, which for the most part follows the one currently favoured by most researchers. Essentially the addition of food proteins is nothing more than a small, but potentially critical, modification of this widely accepted model.

The "infectious agent-diet model" for MS cause is as follows:

1. Infection with one or more childhood illnesses (e.g. Epstein-Barr,HHV-6) results in an autoimmune reaction against tissue in the CNS by molecular mimicry (Wucherpfennig and Strominger, 1995). Such autoimmune reactions are suppressed before any demyelination occurs. However memory cells against the infectious agent are produced and such memory cells can be seen as an autoimmune time bomb because they are also potentially autoaggressive and are much more easily activated than naïve cells (Lovett-Racke et al, 1998).
2. With time, intestinal permeability increases due to various factors including food allergies, alcohol consumption, candida overgrowth and non-steroidal anti-inflammatory drugs (Doe et al, 1979). The consumption of gluten and legumes also increases intestinal permeability through the action of lectins (glycoproteins) (Freed, 1991, 1999).
3. With increased intestinal permeability, intact food proteins begin to escape the gut as do gut bacteria products (Walker and Isselbacher, 1974; Gardner, 1988).These antigens are likely presented mainly by B cells (non-professional APC) and precipitate an autoimmune response by molecular mimicry of the childhood infectious agents and/or self antigens in the CNS. Cordain (1999) has discussed such three way mimicry in celiac disease and the results of both Singh et al, (1989) and Ostenstad et al (1995) indicate that three way mimicry between antigens derived from self, food and infectious agents is a plausible mechanism for the development of autoimmune disease. Such cross-reactions result in the activation of the autoaggressive memory cells which do not require co-stimulation. These initial, rather limited reactions are most commonly successfully suppressed by a reasonably well functioning immune system before any clinically detectable damage is done.
4. The chronic activation of the autoaggressive memory cells by food and bacteria mimics which are escaping through the intestine wall on a near daily basis (MS never sleeps!), combined with major reactivation events precipitated by rare infections, finally results in a failure of the suppressor side and a major autoimmune attack occurs. This is eventually suppressed, and depending on the strength of the immune system and its ability to suppress subsequent autoimmune reactions, the individual experiences a benign course, a relapsing-remitting course (younger, healthier immune system) or a progressive course (older, degraded immune system).

The only difference between this model and the currently favoured model of infectious agent-driven MS is the addition of food antigens which potentially cause small, autoimmune reactions on an almost daily basis. Thus we may have two different modes of autoimmune reactions occurring in MS, one small and frequent (food-driven) and one large and rare (infectious agent-driven). Many geological processes (e.g.

erosion) have a similar duality in terms of magnitude and frequency and many debates have been held on the relative importance of each type of action. Is the landscape mainly shaped by almost imperceptible, day to day erosion or by the powerful 1000 year storm? It is now agreed that both processes play important roles in landscape evolution. Of course for MS it is important at this time to establish if the high frequency, low magnitude process of food-driven autoimmunity even exists and, if it does, whether or not it is of any significance.

I would further suggest that the addition of such food-driven reactions to the model improves its compatibility with the epidemiology of MS. One of the nagging problems with the infectious agent-driven model has been the fact that the geographic prevalence differences for MS are not matched by differences in the prevalence of the various infectious agents postulated to play a role in MS. The major differences in MS prevalence in Australia (McLeod et al, 1994) are certainly not matched by notable differences in infection types, rates or timing. Also it has been documented that MS is more prevalent in inland farming communities than coastal fishing communities when genetics and latitude are held constant and these significant differences are especially difficult to rationalize with the infection-driven model. For example MS prevalence in the outports of Newfoundland is 25/100000 (Pryse-Phillips, 1986) whereas in the farming communities of Alberta it exceeds 200/100000 (Svenson et al, 1994). With genetics and latitude being essentially the same for these two areas of Canada, such a near ten fold difference cannot be easily explained by the infectious hypothesis. However, with the addition of the food antigen factor, which would take into account the dominance of high fat meats, dairy and grains in the Albertans' diet in contrast to the dominance of fish and vegetables of the Newfoundlanders' diet, this major difference in prevalence becomes much better understood. This difference between farming and fishing communities has also been documented in Norway (Swank et al, 1952) and in the islands north of the Scotland (Shetlands vs Faroes) (Fog, 1966) and again the food antigen factor helps to explain such differences.

Required Research - Given that dietary research is required for MS, the next question is what type of research would effectively answer the question of whether or not dietary proteins play an important role in MS. To me I think the best approach would be one or more clinical trials with the subjects using a Paleolithic diet as the therapy. Such a diet emphasizes lean meats, fruits and vegetables and excludes dairy products, grains, yeast and legumes. Other features include a more balanced ratio of fat types, a reduction in salt and sugar intake and no alcohol. The main variable to be measured would be lesion load as determined by serial MRI scans over a one to two year time period. I leave the details of such a trial to those who are experienced in such matters but to me such clinical trials, if properly designed and run, would decide the issue to most people's satisfaction.

I hope that the IOM Committee finds my reasoning compelling enough to recommend research into food antigens and MS. This would constitute extraordinary research (in the sense of Kuhn, 1970) which has been exceedingly rare in the MS research agenda for the past decade (oral tolerance research being a notable exception) (Weiner et al, 1994). There is no doubt we need the normal, inductive science which has completely dominated MS research for decades. However, most breakthroughs in science have not come linearly from such plateau science although such science is absolutely necessary for novel concepts to be conceived in the first place. The suggested dietary research is clearly not safe, predicable research which commonly has little or no impact (most MS research papers are rarely if ever cited). It is risky research which can potentially yield major returns for a relatively small investment.

Conclusions - In summary, I believe there are substantial data and theoretical considerations which make the concept that food proteins play a role in MS progression a very plausible hypothesis. As such, I think such a hypothesis should be tested as quickly and thoroughly as possible with clinical trials being the best research method. The MS research community rarely is presented with a plausible, testable hypothesis for MS progression and it behooves the community and the main funding agencies to act expediently in testing it. Of course those with MS, most of whom are consuming the potentially problematic food proteins every day, would be most interested to know beyond a reasonable doubt if their current dairy and

grain-dominated diets affect the progression of their MS or not. Right now no responsible researcher, including all those on the IOM committee, can guarantee persons with MS that food proteins from such foods as dairy and grains will not affect the progression of their MS. In this atmosphere of uncertainty some persons with MS have even opted for diet revision over use of one of the recommended drugs to try to slow MS progression. I am sure most of the IOM Committee members would not support such an action but until reliable information on diet and MS is available it is impossible to say with confidence if such a choice will be detrimental or not.

Above all else, I think it is imperative that sufficient research be done as soon as possible so that MS researchers and clinicians can provide persons with MS with a definitive statement on the role of dietary proteins in MS. Statements such as "we do not know" and "there is no definite proof that food proteins are involved in MS" (an ambiguous way of saying we do not know) are not adequate and are potentially harmful. I hope the IOM Committee will recommend that sufficient research be done to finally settle this important question which continues to plague many persons with MS and which could open up entirely new fields of research and therapy for MS.

References

Beattie,RM and Walker-Smith,JA,1994, Treatment of Crohn's Disease by exclusion diet. J. Pediatr. Gastroenterol. Nutr., v.19, p. 135-136.

Bodvarsson S, Jonsdottir I, Freysdottir J, Leonard JN, Fry L, Valdimarsson H, 1993, Dermatitis herpetiformis--an autoimmune disease due to cross-reaction between dietary glutenin and dermal

elastin? Scan J Immunol v.38 p.546-50.

Cavallo, M.G., Fava, D., Monetini, L., Barone, F. and Pozzilli, P., 1996, Cell-mediated immune response to Beta casein in recent-onset insulin-dependent diabetes: implications for disease pathogenesis. The Lancet, 348, p. 926-928.

Cheung R. et al, 1994, T cells from children with IDDM are sensitized to bovine serum albumin. Scand. J. Immunol. V. 40, p. 623-628.

Coombs R and Oldham G, 1981, Early rheumatoid-like joint lesions in rabbits drinking milk. Int. Arch. All. Appl. Immunol., V. 64, p. 287-292.

Cordain L, 1999, Cereal Grains: Humanity's Double-edged Sword. World Review of Nutrition and Dietetics, V.84, p. 19-73

Darlington LG and Ramsey NW, 1993, Review of Dietary Therapy for Rheumatoid Arthritis. Brit. J. Reumat., v. 32, p. 507-514.

Doe,WK, 1979, An overview of Intestinal Immunity and Malabsorption. Am. J. Med., V. 67, p. 1077-1084.

Eaton, S.B. and Konner, M., 1985, Paleolithic Nutrition: A consideration of its nature and current implications. New England Journal of Medicine, v. 312, p. 283-289.

Elliott RB, Martin JM, 1984, Dietary protein: a trigger of insulin-dependent diabetes in the BB rat?, 1984, Diabetologia v.26, p.297-99.

Elliott RB et al, 1999, Type 1 (Insulin-dependent) diabetes mellitus and cow milk: casein variant consumption. Diabetologia, V. 42, p. 292-296.

Fog, M, 1966, The Shetland-Orkney-Faroe Project. Acta Neurol. Scand., v.42, Suppl., p. 6-8

Freed DLJ,1991, Lectins in food: their importance in health and disease. J Nutr Med. v.2, p.45-64.

Freed DLJ, 1999, Do dietary lectins cause disease? BMJ, V. 318, p. 1023-1024.

Fukuda Y. et al, 1995, Efficacy of nutritional therapy for active Crohn's disease. J. Gastroenterol., v.30, Suppl. 8, p. 83-87.

Gardner MLG, 1988, Gastrointestinal Absorption of Intact Proteins. Ann. Rev. Nutr., V. 8, p. 329-350.

Haugen M.A., Kjeldsen-Dragh, J. & Forre, O., 1994, A pilot study of the effect of an elemental diet in the management of rheumatoid arthritis. Clinical and Experimental Rheumatology v. 12, p. 275-79.

Honeyman MC, Stone, NL and Harrison LC, 1998, T cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. Mole. Med., V. 4, p. 231-239.

Husby, S., Jensenius, J.C. & Svehag, S.E.,1985,. Passage of undegraded dietary antigen into the blood of healthy adults. Scandinavian Journal of Immunology v.22, p.83-92.

Kaukinen K. et al, 1994, Celiac Disease and autoimmune endocrinologic disorders. Dig. Dis. Sci., v. 44, p. 1428-1433.

Kavanaghi, R., Workman, E., Nash, P., Smith, M., Hazleman, B.L. & Hunter, J.O., 1995,. The effects of elemental diet and subsequent food reintroduction on rheumatoid arthritis. British Journal of Rheumatology v.34**,** p.270-73.

Kuhn TS, 1970, The Structure of Scientific Revolutions. 2nd ed. University of Chicago Press, Chicago.

Lepore, L., Martelossi, S., Pennesi, M., Falcini, F., Ermini, M.L., Ferrari, R., Perticarari, S., Presani, G., Lucchesi, A., Lapini, M. & Ventura, A , 1996, Prevalence of celiac disease in patients with juvenile arthritis. Journal of Pediatrics. V. 129**,** p.311-13.

Lovett-Racke AE et al, 1998, Decreased dependence of myelin basic protein-reactive T cells on CD28-mediated costimulation in multiple sclerosis patients. A marker of activated/memory T cells. J. Clin. Invest., V. 15 p. 725-730.

Malosse, D., Perron, H. and Seigneurin, J.M., 1992, Correlation between milk and dairy product consumption and multiple sclerosis prevalence, a worldwide study. Neuroepidemiology, v. 11, p. 304-312.

Marsh MN, 1992, Gluten, major histocompatibility complex, and the small intestine. Gastroenterology.v.102, p.330-54.

Martin JM et al, 1991, Milk proteins in the etiology of insulin-dependent diabetes mellitus (IDDM). Annals of Medicine, V. 23, p. 447-452.

McLeod JG., Hammond SR. and Hallpike JF., 1994, Epidemiology of multiple sclerosis in Australia. With NSW and SA survey results. Med. J. Aust., V. 160, p. 117-122

Ostenstad, B., Dybwad, A., Lea, T., Forre, O., Vinje, O. and Sioud, M., 1995, Evidence for monoclonal expansion of synovial T cells bearing VÓ2.1/Vß5.5 gene segments and recognizing a synthetic peptide that shares homology with a number of putative autoantigens. Immunology, v. 86, p. 168-175.

Panush, R.S., Stroud, R.M. & Webster, E.M., 1986, Food-induced (allergic) arthritis. Inflammatory arthritis exacerbated by milk. Arthritis and Rheumatism v.29**,** p.220-26.

Perez-Maceda,B., Lopez-Bote,J.P., Langa,C. & Bernabeu,C. 1991, Antibodies to dietary antigens in rheumatoid arthritis--possible molecular mimicry mechanism. Clinica Chimica Acta. v.203,p.153-65.

Pryse-Phillips, W.E.M., 1986, The Incidence and Prevalence of Multiple Sclerosis in Newfoundland and Labrador, 1960-1984. Annals of Neurology, 20, p. 323-328.

Riordan, A.M.., Hunter, J.O., Cowan, R.E., Crampton, J.R., Davidson, A.R., Dickinson, R.J., Dronfield, M.W., Fellows, I.W., Hishon, S. & Kerrigan, G.N., 1993, Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. Lancet v.342**,** p.1131-34.

Scott, F.W., 1996, Food-induced Type 1 Diabetes in the BB rat. Diabetes/Metabolism Reviews, v. 12, p. 341-359.

Singh, V.K., Yamaki, K., Donoso, L. and Shinohara, T., 1989, Yeast histone H3-induced experimental autoimmune uveitis. Journal of Immunology, v. 142, p. 1512-1517.

Svenson, L.W., Woodhead, S.E. and Platt, G.H., 1994, Regional Variations in the Prevalence Rates of Multiple Sclerosis in the Province of Alberta, Canada. Neuroepidemiology, 13, p. 8-13.

Swank RL et al, 1952, Multiple Sclerosis in Rural Norway. Its geographic and occupational incidence in relation to nutrition . New England Journal of Medicine, V. 246, p.721-728.

Walker WA and Isselbacher KJ, 1974, Uptake and transport of macromolecules by the intestine: Possible role in disorders. Gastroenterology, V. 67, p. 531-550.

Weiner HL et al, 1994, Oral Tolerance: Immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens. Annu. Rev. Immunol., V. 12, p. 809-837.

Welsh, C.J., Hanglow, A.C., Conn, P., Barker, T.H. & Coombs, R.R., 1985, Early rheumatoid-like synovial lesions in rabbits drinking cow's milk. Joint pathology. International Archives of Allergy and Applied Immunology v.78**,** p.145-51.

Wucherpfennig, K.W., 1995, Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell, v. 80, p. 695-705.

Zoli G. et al, 1997, A randomized controlled study comparing elemental diet and steroid treatment in Crohn’s disease. Aliment. Pharmacol. Ther., v.11, p.735-740.