

Multiple Sclerosis and Food Hypersensitivities

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Abstract

Multiple Sclerosis is an autoimmune disease in which the immune system causes damage to tissues in the central nervous system. The disease results from both genetic and environmental factors. Studies of identical twins demonstrate that MS develops only in genetically susceptible individuals due to one or more environmental influences.

The epidemiology of MS provides a number of important constraints for the interpretation of the environmental factor which can be regarded as the main cause of MS. The disease has a very uneven geographic extent and occurs mainly in USA, Canada, western Europe, New Zealand and Australia where prevalences are generally greater than 50 per 100,000 population. In these areas there is a noticeable north/south gradient with MS being more prevalent in higher latitude, temperate regions. Also within individual countries there are significant differences in MS prevalence and incidence.

Other important constraints are the sudden increase in prevalence in the Faroe Islands following World War II occupation by British troops and the fact that residency in Hawaii increases the risk of MS for those of Japanese descent while simultaneously decreasing the risk for Caucasians. Studies have also shown that MS cannot be transmitted by person to person contact or by blood transfusion. Finally MS is a modern disease which appeared about 175 years ago. The prevalence has steadily increased from that time.

The various proposed environmental causes of MS can be tested against the epidemiological data base to see if they are compatible with the various constraints. All but one of the proposed causes, including a specific infectious agent (virus, bacteria) and common infectious agents (e.g. influenza virus), can be eliminated due to various incompatibilities with the established data. The only environmental factor which reasonably fits all the epidemiological constraints is diet.

The main disease processes in MS are breaches in the blood-brain barrier and the passage of activated and inactivated immune cells into the CNS. These cells initiate a variety of immune reactions which eventually destroy the myelin wraps on nerve axons. Myelin loss results in various physical disabilities which increase with progressive destruction of myelin.

A diet factor which can result in such disease processes is the ingestion of hypersensitive food. Food hypersensitivities reduce the effectiveness of the blood-brain barrier through Type I (activation of basophils and mast cells) and Type III (deposition of immune complexes) reactions. T-cells are activated against CNS proteins (Type IV reaction) by both molecular mimicry of CNS self proteins by food proteins outside the CNS and by exposure of autoreactive T-cells to previously sequestered CNS proteins following passage of immune elements through a damaged blood-brain barrier.

Abundant anecdotal data indicate that many people have achieved either a permanent remission or a significant slowdown in disease progress through diet revision involving the elimination of hypersensitive food.

The most common foods which result in immune reactions and eventual MS are dairy, cereal grains, eggs, yeast and legumes. These are all foods which have been introduced into the human diet relatively recently and are genetically difficult to tolerate for some individuals.

Introduction

My approach to the problem of MS has been to try to find the most probable cause of the disease by using published data on MS epidemiology (who gets and who doesn't), MS pathogenesis (how the damage to the body happens) and MS recovery (who has recovered from MS and how they did it). The relevant data on MS epidemiology are presented in the first main section. In the next section all the proposed causes are listed and each is tested against the established epidemiological constraints to see if it is compatible with the data or can be rejected as a probable cause. This has led to the identification of a single factor, diet, which satisfies the epidemiological constraints.

The basic disease process (pathogenesis) is presented in the next section. This is followed by a discussion which demonstrates that dietary factors can result in the known disease process. Finally a number of anecdotal accounts of recovery are noted and it is shown that diet revision played a major role in each of these recovery stories.

What is MS?

There is solid evidence that MS is an autoimmune disease which means it is the result of the actions of one's own immune system on specific tissues in the body. For example when the immune system attacks collagen in the joints the autoimmune disease is called rheumatoid arthritis. There are almost 100 different autoimmune diseases with each one being characterized by immune-mediated damage to specific tissues. MS is characterized by chronic inflammation and damage to tissues in the central nervous system (CNS) due to immune responses (Van Oosten et al., 1995). More details of the disease process are presented in a later section.

Constraints on Interpretations of the Cause of Multiple Sclerosis

There are two different aspects to a possible cause of multiple sclerosis. One is a genetic cause and the other is an environmental cause. The importance of both of these factors can be understood when one considers the research which has been done on identical twins. Current data from Europe and North America, which are both high risk areas for MS, indicate that, for identical twins with MS, about 20-30% of such twins both have MS (Ebers et al., 1986; Mumford et al., 1994). This compares with only 2% of affected fraternal twins both having MS (Ebers et al., 1986). The fact that MS is more prevalent in women than men (~1.5/1) also demonstrates the role of genes in MS. Thus there is little doubt that there is a genetic factor in MS and it is likely that only genetically susceptible individuals have the possibility of getting the disease. This interpretation was recently confirmed by Ebers et al. (1995). However, it appears that there is no one dominant gene which determines genetic susceptibility and that many genes, each with a small influence, are involved (Ebers, 1996). Not much more can be said about the genetic factor and the best we can do is accept the fact that it exists.

Importantly the twin data also convincingly show that, in high prevalence areas, only about 50-60% of individuals (5 of 8 identical twins) who are genetically capable of getting MS, actually contract the disease. Thus almost half the people in high prevalence areas who are "genetically programmed" for MS don't get it. In low prevalence areas it would seem that less than 10% of susceptible individuals have MS. This demonstrates that there is at least one dominant environmental factor which results in a genetically susceptible individual being afflicted with MS. These are very important constraints on interpreting the environmental factor which can be regarded as the "ultimate cause of MS". It must be so common that it occurs over much of the world but it has to be very specific such that only half or less of susceptible people are affected by it. Furthermore this environmental factor must be much more prevalent or effective in certain areas of the world.

Another important facet of MS research has been the investigation into the timing of the action of the environmental factor on the individual. Immigration data have been used to elucidate this question (Alter

et al., 1966; Dean and Kurtzke, 1971). It has been determined that adult immigrants retain the risk factor of their country of origin whereas their children tend towards the risk factor of the country they have immigrated to. This has been interpreted to indicate that the environmental factor only affects an individual before puberty (approx. age 15). The more obvious interpretation, that the adults do not experience the same environmental influences as their children do in the new country, was seemingly ignored.

The data on identical twins also provide insight into the question of timing. Twins share essentially the same environment until they leave home (16-21). Thus, the fact that only 25% of identical twins both have MS, is good evidence for the interpretation that the environmental factor comes into play mainly after age 18. Thus we have an apparent paradox. Immigration data apparently indicate the environmental factor acts before age 15 whereas identical twin data indicate that it acts mainly after age 18. Any interpreted cause of MS must explain this paradox.

Another area of research which yields important constraints for interpretation is the global variance in MS prevalence (the number of people having MS which is usually recorded as the number for each 100,000 population) and incidence (the number of people who get MS per year, again recorded as the number for each 100,000 population). As alluded to earlier, the world can be divided into a high prevalence (risk) area which encompasses Europe, Canada, United States, Australia and New Zealand and a low prevalence (risk) area which encompasses the rest of the world (Kurtzke, 1980). In the high risk area prevalences between 50 and 100 per hundred thousand people are common. In the low risk areas MS prevalences are an order of magnitude less (Kurtzke, 1980). This distribution is in part due to the genetic factor because all the high risk areas are dominantly populated by individuals of European origin (Poser, 1994). However, the environmental factor is also responsible for the occurrence of these two very different risk regions. One line of evidence for this is the fact that immigrants to London, U.K. from areas of low risk (e.g. West Indies) have a low prevalence but their British-born children have the same high prevalence as British Caucasians (Elián et al., 1990). An interpretation of the environmental factor must take into account these two different risk areas with the factor being much more common or active in the high risk area.

There are also lower order geographic trends in MS prevalence. One of the most oft quoted trends is the occurrence of a north/south gradient within the areas of high prevalence. For Canada and USA, prevalences are lowest in the southern USA, become higher in the northern states and are highest in Canada (Kurtzke, 1980). In western Europe the gradient is not as well expressed but prevalences are higher in the nordic countries and Britain than in the more southerly Mediterranean countries (Rosati, 1994). The north/south gradient is well expressed in Australia and New Zealand with the highest prevalences in the temperate, southern portions of these countries (Sadovnick and Ebers, 1993). In all these cases genetics cannot explain the north/south gradient and it is clear that the environmental factor is primarily responsible for this general increase in MS in areas of higher latitude. Any interpretation of the environmental factor must be compatible with the north/south gradient of MS prevalences.

MS also shows large differences in prevalence within some individual countries in the high risk area. For example in Norway MS is up to five times more common in the inland farming areas than in the relatively nearby coastal fishing areas (Alter, 1977). Similarly in Canada, MS is at least twice as prevalent in the Prairie provinces (100-225) as it is on the island of Newfoundland (50) (Sadovnick and Ebers, 1993). In these cases genetics has no bearing on this distribution (Newfoundland has a higher percentage of Caucasians) and the environmental factor must be primarily responsible for such drastic differences. This conclusion has been recently confirmed by Rosati (1994) who states in his review of MS in Europe "variations in both prevalence and incidence rates in ethnically homogeneous populations confirm the importance of environmental factors". These macro and micro differences of MS prevalence in the world must be explained by any interpretation of the environmental factor.

Crucial data for constraining the nature of the environmental factor come from prevalences for both those of Japanese and Caucasian descent in Hawaii. Those of Japanese descent have a prevalence of 6.5 (i.e. 6.5 Japanese with MS per 100,000 Japanese in Hawaii) which is over three times that of Japan (2.1) (Kuroiwa et al., 1983; Alter et al., 1971). Conversely the Caucasians who were born and raised in Hawaii have a prevalence of 10.5 which is only one third that of the Caucasians of California (29.9) (Poser, 1994). Thus we have another paradox concerning the environmental factor. In Hawaii it acts such that it adversely affects those of Japanese descent whereas at the very same time it has a very beneficial effect on Caucasians. This puzzling paradox must be regarded as a critical constraint for an objective interpretation of the environmental factor.

One of the most interesting and widely quoted epidemiological studies of MS is that of the greatly increased prevalence of MS in the Faroe Islands (North Atlantic, west of Norway) following the occupation by 1500-2000 British troops between 1941 and 1944 (Kurtzke, 1977, 1980, 1995). Kurtzke has classified this increase as an epidemic although other authors have challenged this view (Benedikz et al., 1994, Poser et al. 1988). Regardless, there can be no doubt that MS prevalence substantially increased in the Faroes following the British occupation. Furthermore, the relationship between MS in the Faroe islanders and the presence of British soldiers is strongly supported by the fact the cases of MS all occurred in islanders who lived close to British bases (Kurtzke, 1980, fig. 15). This is an extremely important constraint because it demonstrates that the environmental factor is not solely indigenous and can be transported from one area to another. Any interpretation of the cause of MS must satisfactorily explain the sudden increased prevalence in the Faroes and the mobility of the environmental factor.

Recently another very important epidemiological study was published by Ebers et al. (1995). These authors were able to demonstrate that children, who were raised in families in which non-blood relatives (step parents, step brothers and sisters, adoptees, etc.) had MS, had no increased risk of MS. This provided good evidence of the genetic factor in MS but more importantly demonstrated that MS is not transmitted by person to person contact. An earlier study which involved spouses of persons with MS also demonstrated this.

Another important piece of evidence for determining MS cause is the fact that there is no recorded case of MS having been transmitted to another person through a blood transfusion (Theofilopoulos, 1995a).

Finally it is important to note that MS is a relatively new disease with the first recorded case being from the beginning of the nineteenth century (Swank and Dugan, 1987). As argued by Swank and Dugan (1987), MS is basically a "disease of modern times" although it is possible a few cases occurred earlier than 1800. There is no doubt that incidence and prevalence of the disease has been increasing over the last century. Thus the cause of the disease must be due to an environmental factor(s) which is progressively having more effect over the last 100 years.

In summary an acceptable interpretation of the environmental factor, which plays a critical role in the onset and progression of MS, must explain the following constraining data.

1. It must be found throughout the world but be specific enough to affect only half or less of the susceptible individuals.
2. It must affect immigrant children more than it does immigrant adults. On the other hand it must affect susceptible identical twins mainly when they are adults rather than when they are children.
3. It must be much more common or effective in northwestern Europe, Canada, United States, Australia and New Zealand than in the rest of the world.
4. It must be more common or effective in higher latitude areas so as to create a pronounced north/south gradient of MS prevalence.

5. It must have enough variation so as to create significant MS prevalence and incidence differences within ethnically homogeneous populations over relatively short distances.
6. In Hawaii it must adversely affect those of Japanese origin whereas at the same time have a positive effect on Caucasians.
7. It must be transportable so as to explain the sudden increase in MS prevalence in the Faroes following British troop occupation during World War II.
8. It cannot be transmitted by either person to person contact or by a blood transfusion.
9. It must be increasingly more widespread and effective over the last 100 years.

The Most Reasonable Interpretation for the Environmental Factor Which Causes Multiple Sclerosis

The nine constraints listed above are key to testing if a proposed cause of MS can be taken seriously or not. Clearly if a proposed cause is not compatible with one or more of these constraints then it must be rejected as the probable cause. Only factors which are compatible with all of these constraints can be considered as a probable cause of MS. All of the environmental factors proposed as a cause of MS have been compiled and these include specific virus or bacteria, common virus or bacteria, heavy metal poisoning, industrial pollution, sanitation, diet, sunlight, altitude, climate (temperature), microwave radiation and cosmic radiation. These factors can be placed into three main groups:

- indigenous factors: sunlight, altitude, climate, cosmic radiation, microwave radiation
- infections: specific virus or bacteria, common virus or bacteria
- transportable, non-infectious factors: heavy metals, pollution, sanitation, diet

First of all, the indigenous factors can be readily eliminated on the basis of the Faroe Islands data. These data clearly demonstrated that the environmental factor is not indigenous but can be brought into an area (e.g. the Faroes).

The infectious causes seem to be the most commonly quoted explanation for the environmental factor. The reason for this appears to emanate from an a priori assumption that unexplained diseases are caused by an infectious agent with viruses preferred over bacteria due to their "difficult to detect" nature. The constraints listed above indicate that it is highly unlikely that either a specific virus or bacteria which infects the CNS is responsible for MS. The main reasons for rejecting a specific infectious agent are:

1. The constraints show that MS is not transmitted either person to person or through a blood transfusion.
2. The significant variation in MS prevalence and incidence in ethnically homogeneous populations over relatively small areas is hard to reconcile with a specific infectious cause of MS.
3. No physical evidence of a specific MS virus or bacteria has ever been found in the CNS of persons with MS despite a very long and concerted effort to find such material (Poser, 1993).

Before leaving this topic it is important to note that the main evidence which is usually quoted by those advocating a specific viral cause of MS is the greatly increased incidence of MS in the Faroes following British troop occupation. The standard interpretation of these data follows Kurtzke (1977) and is that some of the British troops were infected with the MS virus and that they subsequently infected the Faroe islanders. At first glance such an interpretation seems plausible but a more penetrating analysis of the data, coupled with other constraints, makes the viral hypothesis of the Faroes increased prevalence very unlikely.

First of all, there were less than 2000 British troops in the Faroes and, given the 90/100,000 prevalence of MS in Britain, there were, at best, 2 troops with MS. Furthermore, given that any soldier exhibiting neurological disease would have likely been sent home, it is highly unlikely that there were enough troops to infect the islanders. Kurtzke (1995) has countered this argument by claiming that many people may be carriers of the MS virus but not have the disease themselves. There is certainly no evidence of such a phenomenon and Kurtzke's speculation is unsupportable.

Furthermore, as has been mentioned previously, there is no increased prevalence of MS in children with step brothers and sisters with MS or in individuals whose spouse has MS. These data clearly indicate that a specific viral cause of MS is highly unlikely and that any suggestion that one or two British troops transmitted a MS virus to the Faroe islanders is entirely unsupportable.

With the rejection of the Faroe Islands evidence for a viral cause, the interpretation of a specific virus being the main environmental factor which results in MS does not appear to be tenable. This conclusion was also reached by Poser (1993) who stated "the constant failure to confirm the role of a specific organism in the pathogenesis of MS has raised grave doubts about its existence".

It has also been postulated that common viral and bacterial infections cause MS through a phenomenon called molecular mimicry (Theofilopoulos, 1995b). For this to happen a part of the molecular structure of the infectious agent must closely resemble part of the molecular structure of one or more self-proteins in the CNS. Thus when the immune system is activated against the virus it may also attack the similar self-proteins in the CNS. In support of this it has been demonstrated that some viruses do have molecular sequences similar to those of CNS proteins (Wucherpfennig et al., 1995). Also Sibley et al. (1985) demonstrated a weak correlation between viral infections and MS exacerbations. However it must be mentioned that in Sibley et al's study many exacerbations occurred in the absence of infection and many viral infections did not trigger an exacerbation. Also, as shown by MRI studies (Lai et al., 1996), disease activity is essentially continuous in many cases and viral infections certainly are not.

A constraint which strongly indicates that common viral and/or bacterial infections are not the main cause of MS is the prevalence data for Japanese and Caucasians in Hawaii. The prevalence of common infections in Japan, Hawaii and California is very similar, being perhaps highest in Japan due to high population density. Thus, given that MS is three times more common in Japanese in Hawaii than in Japan, clearly demonstrates that common infectious agents are not the main cause of MS. Another constraint which demonstrates that common infections are not the main cause of MS is the north/south gradient of prevalence in many areas. The occurrence of common infections shows little variation within these areas and thus cannot explain such a pronounced gradient. Other constraints, such as the much higher prevalence of MS on the Canadian Prairies than in Newfoundland, also argue strongly against a common virus for the main cause.

Of the transported, non-infectious factors, heavy metals, industrial pollution and sanitation can also be rejected. The most convincing constraint for this conclusion again is the greatly increased prevalence of MS for Japanese living in Hawaii versus Japan where these factors are much more common than in Hawaii. The Faroe Islands data, as well as the much higher prevalence of MS on the Canadian Prairies than in the highly industrialized area of southern Ontario, also are not compatible with these factors.

This leaves us with one remaining factor which is DIET. Diet is certainly not a new interpretation for the key environmental factor responsible for MS although it tends to be arbitrarily dismissed by numerous authors. However a close reading of the arguments against diet leads to the conclusion that diet has not been rejected on scientific grounds, but rather on rhetorical ones (e.g. Sibley, 1992). Statements like "diet has not been proven to affect the disease (McIlroy, pers. comm., 1993)" and "no controlled scientific study has proven without doubt that the course of MS can be modified by dietary changes (Girard, pers. comm., 1991)" are commonly quoted but, in effect, add nothing to the question of the role of diet. Such statements really mean "we have no idea if diet plays a role in MS". Notably no sound scientific argument

has ever been presented against the possible effects of diet. For this analysis, I have looked at diet in the light of the nine constraints detailed earlier. I have found that diet fits all nine constraints and thus I currently believe the main environmental factor which is the prime cause of MS indeed is diet. In regard to the nine constraints:

1. Diet is obviously found throughout the world and it is specific enough to an individual with given dietary habits to result in MS affecting only half or less of genetically susceptible individuals.
2. Diet also provides a reasonable explanation of the immigrant/twin paradox. Adults who immigrate have a strong tendency to maintain the diet of their homeland whereas their children are far more likely to consume more of the food of the country they live in (especially once they have left home). This results in a change of dietary habits and a consequent change of MS risk in the children but not the adults. Thus the immigration data are best interpreted in the light of immigrant children and immigrant parents experiencing different environmental factors in their new country. This is not surprising because it is well known that immigrant children integrate much more than do immigrant adults. Identical twins tend to have very similar diets when they live together at home but their dietary habits potentially diverge after they leave home and live apart. Furthermore identical twins can possibly have separate food sensitivities especially when they are older due to long term intestinal damage and increased permeability. Thus dietary and digestive system changes (and MS risk divergence) would occur in twins mainly after age 18. Thus diet and only diet explains this paradox.
3. The overall diets of the high prevalence areas have certain features in common including high dairy, cereal grain and saturated fat consumptions. These are all much higher than in the low prevalence areas. The great differences in diet between the high prevalence areas and the low prevalence areas can readily account for the occurrence of two very different risk areas in the world. It would appear that the foods consumed in high prevalence areas (e.g. dairy, cereal grains, high saturated fat) are more effective in causing MS as has been noted in various statistical studies (Shatin, 1964; Alter et al., 1974; Agranoff and Goldberg, 1974; Malosse et al., 1992; Lauer, 1994). Shatin (1964) found a good correspondence of MS prevalence with wheat consumption. Malosse et al. (1992) state "We have studied the relationship between MS prevalence and dairy product consumption in 27 countries and 29 populations all over the world. A good correlation ($p=0.836$) was found; this correlation was highly significant ($p<0.001$)". This echoed Agranoff and Goldberg (1974) who almost 20 years earlier had stated "a geographic predisposing factor in multiple sclerosis ... is directly related to milk consumption". Alter et al. (1974) found a significant correlation (0.7) between consumption of animal fats and MS prevalence. Furthermore on the basis of a recent multivariate analysis, Lauer (1994) concludes "The second MS-related bundle comprised characteristics ... with dietary variables (i.e. a diet low in fish and high in dairy products)".
4. Diet is readily compatible with the north/south gradient because diet varies directly with climate and thus latitude. The diets of cooler, more temperate regions include much more saturated fat, dairy and cereal grains which, as discussed above, are the most problematic foods.
5. Significant differences in diet can occur within a given country and these differences are sufficient to account for different prevalence rates. For example, the maritime Newfoundlanders consume much more fish and less dairy and cereal grains than do Canadians on the prairies and, as noted earlier, they have a far lower prevalence than do the land-locked, prairie dwellers.
6. Most importantly diet explains the paradox of the adversely affected Hawaiians of Japanese ancestry and the beneficially affected Hawaiians of Caucasian descent which Poser (1994) characterized as "puzzling". The diet of Japanese-Hawaiians includes many more elements of the high risk diets of Europe and North America (e.g. saturated fats, dairy products, cereal

grains) than does the diet of native Japanese. Thus one would expect a significantly higher prevalence for Japanese in Hawaii. On the other hand the diet of Caucasians in Hawaii includes more elements of the low risk diets (e.g. fish, fresh vegetables and fruits) than does the diet of Caucasians of mainland North America. This of course would result in a lower prevalence for Caucasians in Hawaii. Thus it would appear that diet provides the solution for this puzzling paradox which is inexplicable by other postulated causes.

7. A critical question in this analysis is "Can diet explain the increased prevalence of MS in the Faroes following British troop occupation?" As has been discussed it is highly unlikely that the British brought with them a MS virus but it is clear that they did bring the environmental factor with them. The obvious interpretation is that they brought their own food supplies which would have of course included food high in saturated fat and the foods which most commonly cause hypersensitivity reactions (dairy, eggs, cereal grains, nuts, legumes). The islanders living near the bases (and working on them) would have had easy access to these "non-traditional" foods and added them to their diet. Thus such dietary changes in susceptible islanders can readily explain the sudden increase in MS. These imported foods likely became part of the standard diet of many of the islanders (especially the youth) and this accounts for the ongoing occurrence of MS in the Faroes. Thus diet does indeed provide a solid and reasonable explanation of one of the most specific and well controlled pieces of epidemiological evidence regarding the environmental factor.
8. Diet as the main factor is entirely compatible with the non-transmissible characteristic of MS as noted by Ebers (1996) who, on this basis, clearly stated "In sum these data strongly indicate that the environmental factor is affecting the population risk. Accordingly, factors which influence large populations such as diet deserve careful reconsideration".
9. The diet of the high risk areas (western societies) has changed significantly over the last 100 years with substantial increase of saturated fat, a decrease in polyunsaturated fat and an increase in dairy and cereal grains (Swank and Dugan, 1987). This trend of a higher consumption of these foods has been significantly accelerated over the past fifty years with the rise and constant expansion of the "fast food" (e.g. hamburgers, pizza, donuts) industry. Thus the continued increase of consumption of these foods readily accounts for the steadily increasing prevalence of MS over the last 100 years.

Pathogenesis of MS

In the last section the epidemiological evidence for dietary factors as the main cause of MS was presented. Of course, if diet is the main cause, it must be demonstrable that specific dietary factors are capable of resulting in the various known disease processes of MS. In this and the next sections the basic disease processes (pathogenesis) of MS are reviewed and the theoretical basis for dietary factors resulting in these processes are presented.

The basic pathogenesis of MS involves the entry of immune cells (e.g. T-cells, B-cells, macrophages) into the CNS through the walls of the capillaries and venules (Traugott, 1990; Poser, 1993). Immune reactions occur, a lesion is formed and myelin is eventually destroyed. Myelin consists of fatty tissue which wraps around nerve axons. It essentially acts as nerve insulation and is critical for proper nerve transmissions. Loss of myelin results in degradation of nerve transmissions and a resultant multitude of disabilities which gradually worsen over time as more myelin is destroyed.

It is very important to note that in healthy individuals immune cells cannot pass through the CNS capillaries and venules into the CNS tissue. This does not happen because the walls of the capillaries in the CNS are different from those in the rest of the body in that they have very closely packed cells which

do not allow the passage of immune cells. This special feature of the CNS vascular system is referred to as the blood-brain barrier (BBB) (Traugott, 1990).

It would seem that an intact blood-brain barrier prevents CNS infiltration of immune components and thus stops the possibility of MS occurring. As noted by Compston (1991), one of Britain's leading MS researchers, "blood-brain barrier penetration can be regarded as the primary disease process". This is especially true because many people carry immune cells which are reactive with brain tissue but only a few develop MS. As explained by Soll (1968) many years ago, "isolation (of the CNS) begins to take place during fetal life, very likely before the so-called immunologic "recognition of self" takes place. Thus, at least parts of our brain may be capable of evoking an immune reaction... provided the immune mechanisms were allowed direct access to the CNS". Thus almost 30 years ago it was recognized that a critical disease process in MS is the breach of the BBB and the exposure of the CNS to autoreactive immune cells. This concept is now widely accepted and Theofilopoulos (1995b) notes in a recent, comprehensive review of autoimmune disease "Induction of autoimmune disease, following contact with antigens of such so-called "immunological privileged" sites, has been well documented".

This concept has been supported by observations of MS lesions on MRI scans. On the MRI scans it was observed that the CNS lesions could be enhanced by using gadolinium-DTPA (Miller et al., 1988; Kermodie et al., 1990). Passage of this substance through the BBB clearly indicated that the MS lesions in the CNS occur where the BBB has been damaged so that various substances, including gadolinium, could readily pass through the damaged walls of the capillaries. Furthermore, Traugott (1990) notes "that MS lesions are preferentially localized around postcapillary venules" which have a "relatively low barrier function". This and other evidence led Poser (1987, 1992, 1993), in a series of watershed papers, to declare in no uncertain terms "In order for MS to become a disease affecting the CNS, it is necessary for the blood-brain barrier's impermeability to be altered" (Poser, 1993, p. 53). Recently, this emphasis on the damage to the BBB as a key disease process in MS has been confirmed by Lai et al. (1996). Based on a study of weekly MRI scans in patients, these researchers state that "this finding suggests that breakdown of the blood-brain barrier is an invariable and perhaps obligatory event in the development of new lesions".

A second part of MS pathogenesis, which is more controversial, is the cause and timing of the activation of the autoreactive T- helper cells (a type of immune cell strongly implicated in MS pathogenesis [Traugott, 1990]) which react to the CNS proteins. Two possibilities have been advanced. One hypothesis is that the T- cells are activated in the blood outside of the CNS and these cells then cross the BBB to attack the myelin or other CNS proteins. The other hypothesis, which has been alluded to earlier, is that the autoreactive T-cells become activated against CNS proteins after they have passed through a breach in the BBB and encounter the previously sequestered CNS proteins.

To me it is most likely that many of the pathogenic, autoreactive T-cells are activated outside of the CNS. My reasoning for this conclusion is that MS is just one of many autoimmune diseases and many of the others have only the presence of a normal capillary wall between the blood and the tissue. These diseases require activation of the T-cells outside the tissue and, thus, I believe such a requirement also is the most reasonable assumption for MS.

The cause of the activation of T-cells against CNS proteins outside the CNS is somewhat problematic. The most widely accepted hypothesis (Theofilopoulos, 1995b) is that peptides (fragments of proteins) from foreign antigens which are presented by macrophages (another type of immune cell) to T-cells may resemble parts of CNS self proteins from a molecular structure point of view. This is referred to as molecular mimicry as was mentioned earlier. Experimental data have clearly shown that such a mechanism by both food and viruses can result in the activation of T-cells against various self proteins (Singh et al., 1989; Wucherpfennig et al., 1995; Ostenstat et al., 1995). Thus molecular mimicry would indeed appear to be a critical factor in the pathogenesis of MS.

In summary, the evidence is strong that a key part of MS pathogenesis is the activation of autoreactive T-cells both outside and within the CNS and that persons with MS carry such CNS autoreactive T-cells. These activated T-cells set in motion a series of immune reactions which results in myelin being destroyed by various immune elements (e.g. macrophages) (Traugott, 1990).

Types of MS

One related area regarding MS pathogenesis is that of the outward manifestation of the disease. Most cases of MS start with a relapsing-remitting (RR) character which refers to short periods when new symptoms appear or old ones increase (attack or exacerbation) and long intervals when symptoms improve somewhat or stabilize (remissions). On average it would appear a typical case involves about one attack a year (Sibley, 1992). Notably it has been found through MRI studies that lesion forming activity occurs even during remissions (Lai et al., 1996). Thus in many cases it would appear as if disease activity is essentially continuous with a waxing and waning character.

In many instances RRMS evolves into secondary progressive (or chronic progressive) MS where there are no clear relapses and remissions, only gradual deterioration.

In some cases, MS does not present in a relapsing-remitting manner but rather gradual deterioration begins at onset. This type of MS is known as primary progressive MS.

If untreated, RRMS can have a highly variable course in terms of disabilities although an average rate of decline of one EDDS (a scale for assessing disability state) level every six years has been documented (Swank and Dugan, 1987; Sibley, 1992).

Any proposed cause of MS should be able to explain the various types of MS and the observed average decline rate.

Dietary Factors, MS Pathogenesis and MS Types

As explained in the last section, MS is mainly the result of both the activation of T-cells against CNS protein and damage to the blood-brain barrier which leads to infiltration of immune cells into the CNS tissue and subsequent demyelination. There are two main components of diet which appear to be responsible for the activation of T-cells and BBB damage.

The first and perhaps most critical component is food antigens. Gell and Coombs (1975) described four classes of hypersensitivity which is defined as "an increased state of reactivity that involves a detrimental immune response" (Elgert, 1996). Each of these types of hypersensitivity causes tissue damage through various types of immune reactions (Elgert, 1996). Type I, III and IV hypersensitivity reactions are relevant to this discussion of reactions involving food (Sampson, 1991).

Type I is the classic immediate, hypersensitivity immune reactions which involve the increased production of IgE antibodies upon introduction of an offending food. This is what is termed a food allergy and the reader is referred to Lichtenstein (1993) for a comprehensive review of the immune response of allergens. Note that only this specific reaction is termed allergy and all other reactions are referred to as hypersensitivities. In brief, an allergen in the blood, through a complex series of immune responses, stimulates mast cells and basophils (specific types of immune cells) to secrete various chemicals and hormones such as histamine, leukotrienes and tumor necrosis factor. It is well established that the chemicals secreted by the activated basophils and mast cells can cause a significant increase in the permeability of capillaries (Lichtenstein, 1993). As stated by Rozniecki et al. (1995), "mast cells ... can participate in the regulation of blood- brain permeability". Thus, food allergens are potentially capable of causing significant, localized, increased permeabilities in the BBB. Activated mast cells may also play a significant role in demyelination (Johnson et al., 1988; Kruger et al., 1990). Kruger and Nyland (1995) summarize these concepts: "multiple sclerosis arises due to the effect of the various mediators (histamine

and protease) released from the perivascular mast cells after stimulation by some diet factor". Also of significant importance is that IgG4 antibodies can also activate mast cells and basophils (Shakib et al., 1986; Elgert, 1996). The role of IgG4 in pathogenic immune reactions has been shown by Gerrard et al. (1976) and Rafei et al. (1989). Rafei et al. (1989) found that only 29% of those with food allergies (as demonstrated by food challenges) had positive IgE skin tests whereas 91% tested positive for IgG4 and IgE. Furthermore one patient who demonstrated a delayed response to peanuts had undetectable IgE but markedly elevated anti-peanut IgG4. As recently shown by Bengtsson et al. (1996), non-IgE immune reactions occur in adults due to the ingestion of common foods such as eggs, milk and wheat. IgG4 may well be involved in such reactions.

Type III hypersensitivity involves the production of immune complexes which are formed by the combining of antigens and antibodies. This type of hypersensitivity is likely responsible for many non-IgE reactions. It has been established that these circulating immune complexes can have a pathogenic effect mainly by deposition in blood vessel walls (Cochrane and Koffler, 1973). This causes inflammation of the vessel walls and greatly increased permeability. Immune complexes can also result in the activation of another part of the immune system, complement (plasma proteins), which results in further damage (Elgert, 1996). Thus the increased production of antibodies (mainly IgA, IgG, IgE and IgM), due to the introduction of various food proteins into the circulatory system, can readily result in immune complex formation, deposition in the vascular system of the CNS, activation of complement and a resultant damage to the BBB.

Type IV hypersensitivity refers to cell-mediated reactions and results in the activation of T-cells which then induce an array of damaging immune reactions. These reactions, like Type III reactions, are delayed and often occur days after the offending foods are ingested. The mechanisms by which food antigens induce Type IV reactions are currently poorly understood although such occurrences (e.g. celiac disease in which cereal grain proteins cause cell-mediated reactions) are undoubted. As mentioned earlier, one possible mechanism for foods to induce an activation of T-cells against parts of the CNS is through molecular mimicry. Food proteins which escape into the circulatory system are processed by macrophages which then present peptides (protein fragments) derived from the food protein to T-cells. The molecular sequencing in these peptides may be close enough to the sequencing of self-antigens in the CNS (molecular mimicry) to induce T-cell activation against parts of the CNS. For example it was recently shown that cereal proteins share amino acid homologies with human joint tissue (procollagen) and that T-cells from the joints of arthritic patients were activated by these cereal proteins. Thus molecular mimicry by cereal proteins can result in arthritis (Ostenstad et al., 1995). It is readily conceivable that various proteins found in dairy and grains as well as other foods (e.g. legumes, yeast, eggs) have similar amino acid sequencing as proteins in the CNS.

In summary it is clear that, from a theoretical point of view, hypersensitivity reactions to foods can result in significant damage to and increased permeability of the BBB and can also result in T-cell activation against the CNS. As discussed earlier, such damage to the BBB and activation of T-cells initiates a cascade of immune reactions to happen in the CNS which results in chronic inflammation, demyelination and a diagnosis of MS. The interested reader is referred to the website www.webdirect.net/zeno for a comprehensive discussion of the relationship of food hypersensitivities and disease.

Dietary factors as the main cause of MS also provides a reasonable explanation for the different types of MS. For any individual the ingestion of specific kinds and amounts of sensitive, which potentially affect the BBB and activate T-cells, will vary significantly with time but can have a daily effect. This fact, in concert with random infections by common viruses and bacteria which also affect the BBB and activate T-cells, results in an ongoing disease process but a randomness in the severity of disease activity and the effectiveness of suppressor reactions. This would result in relapsing-remitting character for MS.

As the BBB continues to degrade through time, by the daily irritation by dietary factors and by gradual aging processes (weakening of suppressor reactions), a point is often reached when ongoing disease activity maintains a relatively high level and RRMS transforms into secondary progressive MS.

Primary progressive MS is likely a reflection of an individual's extreme hypersensitivity to various substances combined with high exposure and a relatively easy path for the antigens to reach the circulatory system. In such a case almost continuous BBB failure and T-cell activation might be expected such that suppressor reactions cannot modulate the disease process. Thus MS would progress with no periods of relief.

Thus it would appear as if dietary factors do provide a reasonable explanation for the great variation in presentation and progression of MS.

Anecdotal Data

A final area of potential useful data is anecdotal evidence regarding recoveries from MS or significant positive changes in the course of MS. Such data are quite rightly regarded as "soft" and by themselves provide little, if any, good evidence for interpreting the cause of MS. However, taken from another point of view, these independent accounts of positive changes in MS progression can provide another test of any proposed cause. For example, if dietary factors are the main cause of MS, then it might be expected that diet revision, involving the avoidance of hypersensitive fat food, was a critical factor in many of the documented anecdotal accounts.

To test this I searched for all the accounts of "MS recovery" that I could find in the literature, on the Internet, and through conversations with persons with MS. On the basis of the results of this investigation it would indeed appear that diet revision is a very critical treatment for achieving positive results in the halting or significantly altering the progression of MS. Perhaps the most impressive account of recovery is that of Roger MacDougall (1980) which is described in "My Fight Against Multiple Sclerosis". Mr. MacDougall went from being near blind and confined to a wheelchair to normal health and activity level (for over 35 years) by faithfully adhering to a low fat, food sensitivity-free diet. Other published "success" stories which used diet revision as the main therapy include those of Rachelle Breslow, Alan Greer, Judy Graham, Bob Lawrence, John Pageler and Bryan Forbes. Recently a number of accounts of recovery have been gathered on a website by an individual who himself has recovered from chronic progressive MS (wheelchair confined) to a normal, healthy lifestyle through diet revision.

Of special interest is a scientific paper (Meyer et al., 1954) published over forty years ago when "allergy" was seriously considered as a possible cause of MS. The authors describe 17 case histories of persons with MS whose symptoms were greatly alleviated by avoidance of identified food and inhalant "allergies" (non IgE-mediated). Importantly the authors note that in cases where offending substances were reintroduced that MS symptoms returned.

In another well known study of diet revision, Swank and Dugan (1987) reported that 66 patients who reduced their daily saturated fat intake to less than 20 grams experienced, on average, only very minor deterioration over 35 years. This result contrasted with 31 patients who did not follow such a low fat diet and suffered major deterioration during the same 35 year study. It should be noted that such a low fat dietary regime also resulted in a greatly reduced consumption of the foods which most commonly cause hypersensitivity reactions (dairy, grains, eggs). These impressive results are perhaps the best documented evidence of the beneficial effects of diet revision on the course of MS.

MS and Specific Food Types

It appears that specific types of food are most commonly responsible for causing various hypersensitivity reactions which lead to MS. Such foods are dairy, cereal grains, eggs, yeast and legumes. The evidence supporting this comes from the previously-quoted statistical studies of food consumption and MS

prevalence (e.g. Malosse et al., 1992) and the abundant anecdotal data (e.g. MacDougall, 1980). As noted by Eaton and Konner (1985) these food types, as well as substantial saturated fats have been added relatively recently to the human diet in terms of our two million year evolutionary history. Our distant ancestors did not consume such foods and did not suffer from most of the current lifestyle diseases, including MS, which are now common in Western societies. It would seem that humans are genetically less tolerant of these "recently" introduced foods which cause a great variety of health problems (e.g. heart, stroke, cancer, autoimmune) for genetically susceptible individuals in societies which consume large quantities of them (Eaton and Konner, 1985).

To me the best explanation for the appearance and steady increase of MS in Western societies is the continued increase over the last 150 years in the consumption of the "late, genetically- hard-to-handle" foods such as dairy, cereal grains, yeast, eggs, legumes and saturated fats. Thus, although these "late", potentially problematic foods have been consumed for thousands of years, it is only recently that large quantities have been ingested so as to exceed tolerance levels for many genetically susceptible individuals. Later a suggested treatment for MS is put forward and it is based on the final conclusion of Eaton and Konner (1985) - The diet of our ancestors is perhaps the best defense against the diseases of civilization.

Conclusion

The diverse data sets for MS are all compatible with the hypothesis that diet is the main environmental factor in the cause of the disease. Only diet is compatible with the extensive and varied epidemiological data base. It appears that the activation of T-cells against the CNS by molecular mimicry initiated by food proteins and the constant irritation and weakening of the blood- brain barrier by immune reactions caused by food hypersensitivities eventually result in the onset and progression of multiple sclerosis.

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