A review of the aetiology of multiple sclerosis: an ecological approach

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Summary. Multiple sclerosis (MS) is a disease of unknown aetiology characterised by myelin destruction. Approaches to the aetiology of the condition have noted its differential geographic and demographic distribution; a tentative and inconsistent link with infectious agents; a genetic susceptibility; and a tendency to track with dietary lipids. This review proposes a multidisciplinary approach to the aetiology of MS, emphasising the interlocking and interdependent nature of current aetiological arguments. We suggest that the most profitable interpretation of current empirical data on the aetiology of MS can be accomplished through this kind of analysis.

1. Introduction
The diversity and complexity of aetiological arguments about multiple sclerosis (MS) indicate that an ecological perspective could be of substantial value and importance. Many authors have examined the natural history and ecology of disease (Burnet 1962; Fiennes 1964; Andrewes 1967; Weiner 1971; Southwood 1987).

Ecology is the study of organism(s) including man in relation to their physical and living environments and is the broadest possible way of investigating human disease. Powerful epidemiological techniques developed originally for the study of communicable diseases, especially epidemics, provide the hard scientific data on which to test and generate hypotheses of ecological significance. Chronic diseases viewed in this way are products of the interaction between people and their environments—an ecological perspective. Whether an analysis concerns an individual patient or the prevalence of a condition, people and the context in which they live jointly warrant analysis, rather than only the disease as an entity in itself. The term 'ecology' expresses the principle of the 'multidisciplinary' or
ecological 'systems' approach (Morris 1975). Human ecological approaches to the aetiology of disease especially attempt to understand how specific contributory factors interact as a whole, therefore necessitating interrelated studies in the environmental (both physical and biological), sociological, economic, and anthropological sciences.

Perspectives drawn individually from the major biomedical sciences do not always appear compatible, yet the ecological nature of disease makes it essential that the contribution of each is recognised and understood, before a complete (or more complete) understanding of any particular disease can be developed.

Recent investigations, with a small number of exceptions, have concentrated in isolation on the virological, autoimmunological, nutritional or genetic aspects of multiple sclerosis (for reviews see Bach and Tournier-Lasserve 1987; Lange 1987; Bates 1987; McFarlin and Lachmann 1989), with few studies attempting any coherent multidisciplinary analysis. A summary of the current main disciplinary approaches to the aetiology of MS is given in table 1. Indeed, following earlier single disciplinary approaches to MS, the belief has arisen that the new 'molecular pathology' will solve the aetiology of the disease. This review suggests that such highly focused and single-discipline studies fail to appreciate the multidisciplinary source and relevance of much empirical data on MS.

2. Multiple sclerosis: genes, geography and societies

Fundamental to the development of an ecological paradigm are the observations of Kirtzke (1980) that for people of Northern European and Jewish stock the risk of developing MS depends on where they live; the finding that migration influences the risk of developing the disease (Dean 1967); the report of a point-source epidemic in the Farce Islands (Kurtzke and Hyllested 1979); and the recognition that clusters of cases can occur inside a restricted geographical region within a circumscribed period of time (Dean, McDougall and ElIan 1985; Eastman, Sheridan and Poskanzer 1973).

Genetic inheritance also appears to play a part in susceptibility to the disease. Dick (1975) has calculated that in first-degree relatives the risk is 15 times greater than in unrelated cases although this risk could be attributed to a shared environmental

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<td>Genetic</td>
<td>DNA and recombination</td>
<td>Class II HLA associations e.g. DR2, DR4. Familial studies.</td>
<td>No specific gene or phenotype consistently linked with all MS</td>
<td>Sequence-specific nucleotide probe techniques. T-cell receptor (TcR) gene</td>
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Autoimmune        Gene and/or tolerance defect
Linkage disequilibrium, e.g. DQwl, DQPl
populations. Low penetrance
analysis. TNF genes. Complement genes.
CNS lymphocyte infiltration. T-helper/T-suppressor cell disturbances
No specific antigen defined
T-cell cloning techniques. Characterisation of antigen specificity, e.g. myelin basic protein, gangliosides

Infection        Early childhood and adulthood
Point-source epidemics. Microbial isolates. Antibodies and population serology, e.g. measles virus
> 10 infective agents isolated none specific. Antibodies to ca. 15 viruses detected
Hybridization techniques. Virus-specific nucleic acid sequences in MS tissue

Nutrition        Fetal-neonatal development, adulthood
Geographical and dietary lipid correlations. Low blood essential fatty acids
Diet of MS patients not significantly different from normal control populations
Lipids and neural development. Gene expression-lipid interaction. Lipid modification of inflammatory molecules

HLA, human leucocyte antigens; CNS, central nervous system.

exposure. On the basis of data in familial studies of MS, the existence of a suspect gene which may be carried by 20% of the population is a possibility suggested by Stewart et al., in 1981 (Stewart, McLeod, Basten and Bashire 1981). Other family and twin studies provide evidence for genetic association which is probably multi-factorial and related to immune regulation (Kuwert 197-7; Williams, Eldridge, McFarland, Hauff, Krebs and McFarlin 1980; James 1985). Moreover, recent evidence using molecular probes (McFarlin and Lachmann 1989) also suggests that MS is polyg@c and involves possibly three or more genes, including immune response genes. In summary, the human leucocyte antigens HLA-A3, HLA-B7 and HLA-DR2 show associations with MS, with the strongest association being for DR2. Therefore, if a specific HLA allele is directly involved in the aetiology of MS, the most likely candidate would be DR2. However only 500/o of the US and northern European MS cases carry DR2 and DR2 is not associated with all MS populations. Moreover, the frequency of DR2 is higher in some low-risk MS populations such as the Japanese in comparison with European caucasians. The possibility exists that there is a linkage disequilibrium with another gene such as DQwl (Francis, Batchelor, McDonald, Hern and Downie 1986), which may have aetiological significance. However, these genetic factors may be of less significance than rearing and working environments because prevalence is different in particular genetically sin-dlar groups living in different environments, e.g. the Faroese and the Shetland Islanders, and there seem
to be different risks associated with different socio-economic patterns. Moreover, genetic analysis and comparative studies between cross-cultural populations (especially low-density populations) must be approached with special care because of social complexity such as the widely documented nonrandom associations in mating patterns in human societies (Flinn and Low 1986). This is demonstrated, for example in, inter- and intra-cross-cultural studies of Ashkenazi Jewish, Muslim Jordanian, Kuwaiti and Palestinian populations, peoples often studied in relation to NIS.

The global distribution (figure 1) of MS tends to favour an environmental view in which the results of patterns of migration suggest that any transferred genetic susceptibilities are of relatively low importance compared with acquired environmental factors. For example, Poskanzer, Walker, Prenney and Sheridan (1981) indicated that north-west European whites in the USA have a considerably lower risk of developing the disease compared with that of genetically similar people living in their countries of origin. Kurtzke (1980) has stated that MS can be regarded as the white man's burden spread from Western Europe not only through the distribution of a pool of genetically susceptible stock, but through the distribution of dietary and other environmental patterns leading to an enhanced risk under certain conditions.

Although accurate case ascertainment in epidemiological and other surveys of MS is handicapped by diagnostic difficulties, case finding and the course of the condition (Acheson 1977)-a similar problem to that existing in relation to clinical trials (Robinson 1987)-the results from many studies point to general associations of factors with the distribution of the disease. Thus more females than males (1.5:1) acquire the disease. Significantly higher proportions of people with MS were found in social classes I and II by Russell (1971). However, age at onset, and occupation show a tendency for males in social classes III, IV and V to manifest the disease earlier than those in groups I and II (Russell 1971). An excess of farmers and agricultural workers from the Northern Ireland register of MS has been reported (Kurtzke 1986, 1971). In southern Australia there is mounting evidence that prevalence is high when childhood is spent in rural areas (Murrell Donoghue and Ellis 1986). There is a clear latitude relationship to the
prevalence of NIS in Australia (McCall, Brereton, Dawson, Millingen, Sutherland and Acheson 1968; Hammond, McLeod, Millingen, Stewart-Wynne, English, Holland and McCall 1988a). This association is reflected in the standardised mortality ratio (SMR) rates over a 10-year period for sheep and dairy farming areas of south-eastern Australia (figure 2). However, in western Australia, MS prevalence is higher in urban Perth than in agricultural areas, although early habitat was not specifically considered in the study by Hammond, Stewart-Wynn, English, McLeod and McCall (1988b). In this respect there is some evidence that patients tend to migrate from country to city after the onset of the disease to be near specialist clinics, and other supportive facilities.

The limitation of many epidemiological studies is that they have focused on prevalence according to place of birth or place of residence at onset or death. There are, however, a few studies with environmental or ecological data on habitats between 0-15 years of age when acquisition of the disease is thought by some to occur (Dean 1975). However, the conclusions of Dean are based on an analysis of very few cases and could be misleading. Nevertheless, it has been suggested that there are two points of vulnerability, at least 21 years prior to onset and shortly before or at onset,
supporting the notion that the induction of MS is a two-stage process (Alter and Okihiro 1971; Poskanzer et al. 1981).

The relatively higher risk of rural as opposed to urban populations, has been further emphasised in a range of studies. Shepherd and Downie (1978) found that in north-east Scotland the risk of developing MS appeared less if birth occurred in a large urban centre. The same observations were made earlier outside of Belfast in Northern Ireland by Ashitey and Millar (1970), although these were not supported by urban-rural differences in north-east England according to birthplace. In early studies of MS prevalence, Swank, Irsted, Strom and Backer (1952) found that rates were high in Norway among rural populations and an apparent increase in MS was reported among rural Danes during the war. Prevalence rates in Finland (Kinnunen 1984), Poland (Cendrowski, Wender and Dominik 1969), Czechoslovakia (Lensky 1979) and Switzerland (Georgi et al. 1979) seem to be highest where dairy-farming activities take place. In the county of Hordaland, a dairy-farming district of western Norway, a threefold increase in MS occurred between 1963 and 1983 identified by Larsen, Riise, Kvaale, Nyland and Aazii (1984). These indications of clustering according to year of onset were observed in rural areas and support the concept of an environmental agent in aetiology. Although many of these individual studies are open to methodological criticism, the relatively consistent direction, the reports of associations between dairy farming, rural environments, and MS is striking.

The role of environmental factors in the genesis of the disease also appears to be substantiated in communities in the Shetland/Orkney Islands which have the highest incidence of MS in the world, although the incidence now appears to be declining in the Orkneys. In an earlier search for an environmental agent, a case control study demonstrated differences in sanitation, place of residence at onset and animal exposure (Cook, Cromarty, Tapp, Poskanzer Walker and Dowling 1985). Could exposure to raw farm products be changing particularly in relation to unpasteurized milk consumption? The case control study identifying this association appears to answer this question and supports the milk association study undertaken in New Zealand by Butcher (1976). An alternative or complementary hypothesis to account for the high incidence of the disease in the Shetland/Orkney Islands is that historic population migrations of those with susceptibility genes for MS have led to the current substantial rates of the condition. However, such a hypothesis would tend to be associated stable rather than changing incidence in relatively isolated communities.
Figure 2. Representative high and low SMR's for MS in statistical divisions in rural/urban areas of Eastern Australia (excluding major cities) for a 10-year period (1969-1978; unpublished data). Shaded areas signify high SMR, unshaded areas low SMR.
Occupational associations with MS continue to suggest a substantial role for environmental factors. There have been few studies of MS by occupation (Amaducci, Arfaioi, Inzitari, and Ivlarchi 1985; Murrell 1988; Murrell and Matthews 1990). They identify a raised risk for leather workers. The most recent study identifies a range of occupations in the UK with significantly raised SMRS, which are represented schematically in figure 3. These trends were not the same for carcinoma of the colon or ischaemic heart disease. In this study wives of farm managers and farm workers appeared to be at greater risk than wives of butchers and meatcutters and, although some of the data is based on low case numbers, it is the overall trend and direction of the findings that is important.

Increased contact with a farm or raw farm products could fit with the mathematical models of MS proposed by Alter, Loewenson and Horshe (1973) in those communities reporting high prevalence. An example of such a deduction is the farm contact histories reported in the earlier association of MS with distemper of dogs in Iceland reported by Cook, Gudmundson, Benediks and Dowling (1980), although the distemper and dog ownership hypothesis is now thought unlikely in the aetiology of MS (Krakowa, Read, Nassim, Smith, Patterson and Warlow 198@; Miele, Mathes and Matzier 1983). In one twin study by Bolsowick, Kurtzke, Brody, Hrubic and Gillespie (1978), contact with farm animals was found to be a significant environmental variable. The outbreak of MS in laboratory workers involved with research with brains from sheep dying from swayback by Campbell, Daniel, Porter, Russell, Smith and Innes (1947) is particularly interesting and relevant to this notion, especially now that confirmation has been updated (Dean, McDougall and Elian 1985), and the fact that swayback itself is due to a copper deficiency.

Sosa, Font De Mora, Navarro (1987) have suggested that the so-called 'MS epidemics' only occur on islands; a fundamental problem with this hypothesis is that prevalence for some of the island populations in their study is based on low case
numbers; for example, Gozo 3 per 25,000 and Malta 14 per 25,000. The disappearance of the point-source epidemic of MS on the Faroe Islands following the departure of a garrison of 8,000 British troops there during World War II is, however, worthy of speculation. Could this have been due to a change in the Faroese children's contact with raw farm products imported from ports in northern Scotland or the Shetland/Orkney Islands during this period of social change? Or could it be due to earlier human migration patterns, and a shift in the relative gene frequencies in the Islands' population? Or both? There is a relatively low incidence of MS in the Faroese compared with the Shetland/Orkney Islanders even though both are of Scandinavian genetic stock, but, interestingly, fishing has remained a very significant component of Faroese life whilst the Shetlanders have adopted British agricultural practices (Allison 1963).

It is important to note that trade communications for the Faroese were resumed with Denmark in the post-World-War-II period. An examination of ordnance and catering records of these occupation forces may also offer some clues on the role of environmental factors in the aetiology of MS. For example, the practice of giving free milk to children, as in Britain, may have been implemented or meat imports may have come from Scotland or the Shetland/Orkney Islands.

Despite the clear evidence of some genetic factors with the aetiology of NIS, there are substantial data indicating a fundamental role for environmental factors. In addition, the cumulative evidence of many studies point to the relationship of dietary factors to the onset of the disease.

3. The associations of diet with the aetiology of MS

The early work by Alter, Yamoor and Harshe (1974) and Arganoff and Goldberg (1974) indicate strong ecological correlations between the nature of dietary lipid and MS. In this context the geographical distribution of MS has also been likened to that of cancer of the colon (Wolfgang 1975). The conclusions from these studies have been that a high dietary intake of animal meat and fat and high socio-economic status are linked to MS. In Asia and Southern Europe where such consumption patterns are low, MS is uncommon. As noted earlier, it has been suggested that some of the local foci of high prevalence in some areas might be related to farming and dairying communities or milk consumption. For example, the intake of dairy fat has been reported to correlate with MS mortality (Dick 1976). One explanation of the geographical distribution of MS suggests that dietary deficiencies or imbalances of essential and non-essential fatty acids during neural development leads to defective neural membranes (Crawford and Harbige 1987, Bemshon and Stephanides, 1967).

What may be of interest here is that, although the specific events associated with the development of the nervous system and specifically with the initiation of myelination are not well understood, they are thought to result from an interplay of nutrients (Neuringer, Anderson and Connor 1988; Ward, Durrant, Sankey, Bound and BryceSmith 1990), regulatory genes (Hunt 1977), specific effects of hormones (Bottenstein, Sato and Mather 1979) and neurotransmitters (McMorris 1977). MS may be associated with absent or defective genes, or regulatory genes important to the structural and biochemical integrity of myelin, and or associated with suboptimal intakes of nutrients during the development of the nervous system necessary for the chemical and biological stability of myelin. Clausen and Moller (1967), later confirmed by Selivonchick and Johnston (1975), have shown that rats deficient in polyunsaturated fats during the development of the central nervous system (CNS) have an increased susceptibility to experimental autoimmune encephalomyelitis (putative animal model for MS). Neural and associated endothelial membranes may, therefore, be more susceptible to decreased stability and breakdown, infectious, or toxic immune-inflammatory insult due to the early nutritional environment, with subsequent neural antigen exposure to the immune system with immunogenetic restriction.

Low birthweight with disturbed neural development can be considered a fetal form of malnutrition, and in the Western world is likely to be due to essential fatty acid and elemental nutrient insufficiency or antagonism.
(Crawford, Doyle, Drury, et al. 1989; Ward, Durrant, Sankey, Bound and Bryce-Smith 1990), rather than protein and calorie nutrition. An interesting finding in relation to this point is that the Faroe Islanders fish-based diet has been causally linked to their higher birthweights and longer duration of pregnancies (Olsen, Hansen, Jensen and Sorensen 1989). A comparison with the Shetland/Orkney Islanders who, it has already been noted, generally follow British agricultural practices and have a higher incidence of MS, might uncover a relatively high incidence of low birthweight as in the UK as a whole. It is also this low birthweight group which shows impairment of immunological function (Chandra 1976, Moscatelli, Bricarelli and Piccinini 1976). Research on the relationship between low birthweight, the incidence of childhood infection in such a risk group, and the later development of MS would provide further clues as to the credibility of this possible linkage.

If MS is an immune-inflammatory type disorder (Adams 1989) then the dietary lipid-MS association could also be highly significant; because there is now increasing experimental and epidemiological evidence for an involvement of lipids in these disorders (Kromann and Green 1980; Homsy, Morrow and Levy 1986; Moncada and Salmon 1986). Furthermore, the apparently increasing incidence of MS in Japan (Satoyoshi, Saku, Sunohara and Kinoshita 1976)-if it can be substantiated-and the indications that Japan's changing dietary habits towards more westernized patterns (Tamura, Hirai, Terano et al. 1986) especially in terms of lipid, may be highly significant. Also of interest here, is the reported war-time decline in MS in some Scandinavian countries (Swank 1950) which for a 'degenerative disease' seems surprisingly rapid. However, such a decline would be consistent with an inflammatory process.

A further factor may be a postulated intrinsic defect affecting cellular membranes (including cells of the immune system) as well as an inborn error of fatty acid metabolism, possibly accentuated by dietary factors (Thompson 1973; Field, Joyce and Smith 1977; Baxeyanis, Reclos, Fagos, Doufexis, Papageorgiou and Papamichail 1987). Recent studies by Harbige, Jones, Jenkins, Fitzgerald, Forti and Budowski (1990) suggest that the reported abnormalities in, for example, blood cell surface charge and depleted/lowered blood essential fatty acids can be corrected by nutritional means. Extensive evidence suggests that, apart from, and in addition to, immunity in infectious diseases, genes exist which confer inherited resistance or susceptibility to the infectious, as well as nutritional, diseases termed metabolic polymorphism (Motoisky 1960; Roberts 1985; McNicholl 1986). These could act as selective ecological genetic factors and, therefore, account for the associations of MS with genotype, although our understanding of the ecological genetics of MS have been little studied and are far from complete.
4. The association of infection with the aetiology of MS

A combination of the dietary concepts already cited, and the concept of infection could explain a large component of the epidemiology of MS. An infective agent needs to meet certain criteria in the case of MS. It needs chronic persistence with multiple exposures causing minimal systemic disturbance. In addition, the disease process has to be focal, relapsing and remitting, reflecting known lymphocyte responses. There should be a depression of specific T-lymphocyte (T-cell) phenotypes in the circulation and a depression of natural killer T-cells in the CSF. The CSF should have oligocional antibodies and there should also be a perivascular mononuclear leucocyte infiltration in the CNS (Waksman, 1981).

These criteria in part rule out most viral, and totally exclude many pyrogenic bacterial agents, although include organisms such as spirochetes or unicellular parasites. African trypanosomiasis meets the above criteria, as do sarcocystis and toxoplasmosis. Whilst trypanosomiasis may be excluded on basic ecological criteria, e.g. tropical vs. temperate distribution and vector ecology, other putative candidates may be identified which are relevant to this argument.

Koprowski, De Freitas, Harper, Sandbert-Wollheim, Sheremeta, Robert Juforr, Sazinger, Feinbert, Wong-Staal and Gallo (1985) in studies on Florida (USA) and Swedish MS population groups have suggested that some MS patients respond immunologically to, and have cerebrospinal T-lymphocytes containing, a retrovirus that is related to, but distinct from, the three types of human T-cell lymphotropic viruses, e.g. HTLV I-III. No uniform response to one particular type of HTLV was observed. A related but distinct retrovirus might be expected to cross-react weakly with one or more antigenic and genomic determinants of the known HTLVs just as a weak cross-reactivity with HTLV-1 probes led to the discovery of HTLV-2. However, these results have not been confirmed by a French research group investigating MS populations in France (Paris) and the West Indies (Martirique) (Gessain, Abel, De The, Vemant, Raverdy and Guillard 1986). This disparity may reflect varying socioecological contexts and basic geographical differences.

The experimental results of Carp, Merz and Licursi (1972, 1973) are intriguing in relation to the involvement of an infectious agent in MS. They showed that there is a factor in the majority of MS (issues which consistently causes a significant decrease in polymorphonuclear neutrophils (PMN) in the peripheral blood of inoculated mice. This factor was in high titre in a pool of MS brains; transmitted from mouse to mouse with extensive replication, and the size of the factor causing the change was less than 50 run and found in the lysate of cells 18 passages after exposure; however, attempts to repeat these findings in many other studies have not been successful.
In a number of studies (see the review of Fraser (1975)) a consistent finding has been the slight elevation of measles virus-specific antibodies in the sera of MS patients. More recent studies by Hankins and Black (1986) suggest that MS patients responded differently to M protein (one of the five measles-virus structural proteins) showing a depressed antibody response as compared with controls, suggestive of altered immune responses to this virus.

Studies on CSF samples from MS patients have now shown elevated antibody (AB) levels not only to measles virus but also to adenovirus, mumps, influenza type C, varicella, respiratory syncytial virus, parainfluenza 3 and in serum to Epstein-Barr (EB) virus, whilst many of these are known B- Lymphocyte polyclonal activators, triggering non-specific antibody production. It is therefore not surprising that AB production against many of these common viral infections is seen during relapse, and in non-relapse MS patients (S", Arnadottir, Reunanen and Ilonen 1983; Waksman 1985; Bray, Bloomer Salmon, Bagley and Larsen 1983). Many of these viruses, i.e. measles, influenza, adenoviruses and EB virus, also have homologous peptide sequences to encephalitogenic regions of myelin basic protein (Waksman 1985) and may therefore be of importance in the pathogenesis of MS.

However, despite these virological findings, Poskanzer, Sever, Sheridan and Prenney (1980a) failed to show any consistent elevated antibody titres or the presence or absence of antibody for 17 viruses (including measles) in the serum of MS subjects in the Orkney and Shetland Islands where the rates of MS are the highest recorded. The roles of these individual viruses and their involvement in the aetiology of MS thus remains unsolved.

Other studies of potential viral agents such as that of Cook and Dowling (1977) raised the possibility of an association between house pets and MS in a careful study of MS patients and controls matched for age, sex, neighbourhood and socioeconomic status. No difference in ownership of cats or dogs was found. However, exposure to small indoor pets (cats or dogs) was significantly higher in the MS group which was more pronounced during the 10 years before onset of initial symptoms. Following the review of related research earlier in this analysis, attention to the diet of the animals, particularly in the use of raw meat, would have been of interest, but is not indicated.

Serological studies have failed to incriminate canine distemper virus in the aetiology of MS, a viral hypothesis referred to earlier in this review, although measles antibody titres were significantly elevated (Krakowa and Koestner 1978). Viral infections can enhance a simultaneous Toxocara cants infection. T. cants is a nematode parasite of dogs, in which man becomes an incidental host when blindness, especially in young children, may occur (Payri 1975). The absence of reports to T. cants larvae in tissues of MS patients should not disqualify this association because of the
difficulty of finding these agents (Woodruff 1970). However, a study by de Savigny (1980) in a UK MS population indicates there is no significant difference in toxocaral antibody titres in MS patients compared with healthy controls using an enzyme-linked immunosorbent assay (ELISA) system. Toxoplasmosis is a meat-cat-man transmitted disease (McCabe and Remington 1988) which can cause neural tube defects, abortions and is opportunistic for AIDS victims but has not been implicated in MS. Both nematode and protozoan infections could act as vector species for other micro-organisms of significance to MS pathogenesis and, therefore, could account for the MS associations with dogs, cats, animal meat and milk.

The occurrence of oligocional IgG antibody responses within the CNS initially was described by Laterre (1965) to include MS, syphilis, SSPE and parasitic diseases of the CNS (e.g. trypanosorniasis). These responses reviewed by Norrby (1978) have been encountered in cases of herpes encephalitis, mumps, meningitis and chronic progressive rubella panencephalitis. The finding of anti-Sarcocystis spp. antibodies in 34/o of humans tested, including 9 out of 24 with cases of MS, indicates a frequent exposure to this parasite which could be relevant to CSF IgG production (Murrell, O'Donoghue et al 1986), in Australian MS patients.

It is known that soluble extracts from various Sarcocystis spp. exhibit neurotoxic activity via unknown mechanisms when administered to laboratory animals (Hiefe, Litzke, Scheibner, Jungmann, Hiefe and Montag 1981). However, O'Donoghue (1978) has found that the adult parasites are notoriously difficult to find in the brain tissue of affected animals.

A review of the literature suggests that MS may be clinically indistinguishable from some presentations of neurobrucellosis (Abramsky 1977; Arbrisseau, Maravi, Aguilera and Martinez-Lage 1978; Nenycz-Grabiec 1981; Zelachowska, Nenycz-Grabiec and Zietara 1984). In addition, the CSF findings of MS and neurobrucellosis appear comparable (Arbrisseau, Maravi, Aguilera and Martinez-Lage 1978; Silva, Rio, imaiaGoncalves, Pereira, Paimeira, Brito and Cruz 1980). The occupational SMR data have reactivated the debate (figure 3), and weak Br. abortus agglutination have been found in 44% of MS subjects in Australian studies (Murrell 1988; Murrell and Matthews 1990). However, there are six species of brucella affecting cattle, sheep, goats, dogs, pigs and rodents, with 19 biotypes between them and, although there is a certain amount of cross-reaction in testing, not all biotypes will agglutinate with the Br. abortus suspension (Thrimm 1982). The geography of MS in southern Australia raises the possibility of a Br. ovis association (figure 2). It may also be possible that specific T-cell lymphopenia occurs with brucellosis (Razziuddin, Bilal and Benjamin 1988), meeting another criterion for MS.
Of current extensive research and public interest, and by way of illustration of the general point, is the neurological disorder of adult cattle bovine spongiform encephalopathy (BSE) with the apparent transmission of the infective agent via animal products (Southwood, Epstein, Martin and Walton 1989), giving a contemporary example of the many animal-meat and other product associations with infectious agents.

The pattern of oligoclonal IgG remains remarkably constant even after several decades in individual MS patients so that a continuous production of viral or other antigens must be assumed. The inability to culture detectable virus from MS brain suggests an alternative non-specific immune activation of immune competent cells which at one time produced antibodies. Therefore, oligoclonal IgG in CSF probably has many sources, because of the presence of oligoclonal IgG in the sera of patients with many diseases (Michaux and Heremans 1969).

A relationship between neurosyphilis and MS was firmly believed at the beginning of this century. Spirochetes morphologically distinct from Treponema pallidum in acute plaques were identified by Steiner (1954), but were later considered to be an artefact. Such an agent has been reappraised and an association between MS and chronic relapsing sinusitis established (Gay, Dick and Upton 1986). A hypothesis that an oral spirochete is responsible appears to show promise linked with this observation (Gay and Dick, 1986) in UK MS populations.

A complementary hypothesis that could account for the many reported associations of MS with infective agents is the suggestion that MS is a disorder of immune regulation (Waksman and Reynolds 1984) and, therefore, predisposes to infectious agents. This hypothesis could then account for the many different infective agents being associated with MS.

One thesis to explain the isolated or global distributions of the disease is an exposure to neurotoxins (chemical or biological) or an active infective agent acquired from unpasteurized milk, raw or undercooked meat. One such toxin which breaks down the blood-brain barrier and causes ataxia and blindness in sheep is the epsilon toxin of Clostridia Perfringens type D. Focal symmetrical encephalomalacia (FSE) results (Harticy 1956; Griner 1981). Lesions are brain stem and periventricular in site. Finnie (1983) demonstrated that the epsilon toxin binds endothelial cells in brain blood vessels causing endothelial leakage and demyelination.

The striking feature of the topography of the plaques in MS is the regular occurrence of periventricular lesions in chronic cases (Peters 1968; Lumsden 1970) as in FSE. Wolfgram (1979) suggested that: 'there is a noxious agent exuding from the vascular system-underlining the perivenular nature of demyelination where blood flow will be slowest'. This hypothesis is not new but a reconstruction of older theories which postulated that the demyelination in MS is caused by a circulating
compound of low molecular weight. It is of interest that in another clostridial toxic disease, enteritis necroticans in humans (pigbel) caused by the beta toxin of Clostridium perfringens type C, at least five multivariate aetiologic events were necessary if any one individual was to acquire significant pathology (Murrell et al. 1966, Murrell, 1982, 1983). Such a process may well be operating in the case of MS.

That complex social systems might help to explain many infectious associations referred to above in different MS communities can be illustrated with reference to poliomyelitis before vaccination existed (Poskanzer, Shapira and Miller, 1963). Immunity to the virus is established given through contact within the first 3 years of life. However, in modern societies very young children have been largely protected from sources of infection. Nonetheless, without vaccination they would often become exposed after contact with their peer groups on starting school. At this age, not only would they be susceptible to infection but would be more likely to develop clinical manifestations of the disease. This is a well-known example of an infectious disease (poliomyelitis) showing clinical expression largely due to social ecology. Kuru, hepatitis B and HIV are other well-documented examples arising through complex patterns of social interaction; less well-known diseases have been described by Marshall (1973). Thus despite the inconclusive nature of much research on a possible infectious aetiological agent in MS, there is indicative evidence from a number of directions that such an agent(s) is a distinct candidate as part of a multifactorial approach to the disease.

5. Conclusions
In summary, a variety of ecological arguments are presented in this paper which together, suggest that multiple sclerosis is multi-factorial in aetiology. Non-specific infections, probably different for geographically and culturally separated MS populations and operating in the presence of dietary lipids, suspect genes and socioeconomic factors, are all ecological variables interacting selectively in patterns deserving intensive study. Critical exposure to these variables is thought to occur during the 0-15 year age period when, in addition to genetic influences, maternal and early diet, susceptibility to infectious agents, hormonal changes, and socioeconomic factors play such an important role in genesis of human disease.

Further research should be directed at exploring the habitat, social behaviour and maternal and early dietary patterns of groups of individuals with and without a theoretically increased MS susceptibility. The established latitude line with MS in white Australians points to the need for comparative studies of MS in aboriginal Australian populations. Detailed anthropological studies indicate wide social and biological differences between nomadic northern Australian aboriginals and southern westernized (settlement) aboriginals (Weiner 1971; Mdehan 1977) which
could, in principle, give rise to a differential incidence of MS in these communities. Studies should also be undertaken in appropriate genotypes and in communities where the contact with, and consumption of, raw dairy farm products is high (e.g. the Falkland Islands). Studies of SMRs in those occupations particularly exposed to such factors should be expanded. Similarly, there is a need for the further acquisition of data on MS prevalence in lifelong vegans and ovolactovegetarians and on the dietary patterns of mothers of MS patients. Epidemiological investigations of MS incidence in Japan, now that dietary patterns seem to be changing, especially essential fatty acids, and total lipids (Tamura et al. 1986), need increased priority. In this respect migration from Japan to the USA has been studied in relation to the effects of nutrition (lipids) on other conditions such as coronary heart disease and cancer demonstrating strong associations as dietary patterns change. Similar comprehensive epidemiological research on MS, including MS prevalence in American-born Japanese, could produce more valuable data on for example a 'vulnerable nutritional window' for MS, perhaps through the effect of maternal or early childhood diet, and in relation to new infectious agent exposure and relative MS risk. Well planned and extensive ecological investigations of the Faroe in comparison with the Shetland/Orkney Islands should also be undertaken.

In conclusion, this analysis has demonstrated the importance of what has been described as an ecological approach to MS. The different disciplinary foci of interest in relation to MS, considered as they most frequently are in a relatively insular way, do not do justice to what it is becoming clear is a condition with a multifactorial aetiology. This multifactorial frame of reference is most profitably embodied in the study of MS as a disease resulting from an interaction between people and their environments. It seems likely that the most significant progress in understanding the aetiology of this condition will follow from an appreciation of its ecological context.

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