Environmental associations with the risk of multiple sclerosis: the contribution of ecological studies

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Although the role of genetic factors in the etiology of multiple sclerosis (MS) is presently undisputed there is a general consensus that exogenous factors play the major role. In a rather conceptual way one can subdivide the human environment into a number of fields which are by no means truly separated from each other. Commonly these are categorized into a geoclimatic and a sociocultural compartment, but even between these two compartments considerable overlaps exist. For example, a natural feature easily changes to a sociocultural one by exploitation and specific use by man. Substantial variables within the individual fields can operate by quite different mechanisms, including toxic-metabolic and/or immunological paths, but they might also be vectors of infectious agents. Thus a strict fixation on one or another of these two basic mechanisms of causation cannot be made by epidemiology, as long as no clear knowledge is available from clinical or experimental research. In addition it should be kept in mind that epidemiology is almost exclusively able to generate and to support hypotheses; final confirmation has to be left to the basic disciplines.

Criteria for causal inference in epidemiological research have recently been reformulated by M. Susser (1). Especially noteworthy is the important criterion of consistency in terms of *replicability* and of *survivability*, the latter term meaning the achievement of the same result under varying methodological conditions. Another important aspect is *statistical coherence* in the form of a dose-response gradient, whereas specificity of the association is no longer considered a strict prerequisite for causality (2).

Methodological problems of the ecological approach with special reference to MS will be treated in a subsequent paper (3), and only some aspects shall be mentioned here. Beside easy performance, the lack of recall and selection bias for example, and high external validity, the fact that consistency is easy to be demonstrated is a clear advantage, and a test for a dose-response gradient is already inherent in the basic study design. There are, however, well known shortcomings: the individual risk is not tested, and many confounders are in play. As Greenland & Robins (4) pointed out, ecological confounding can be independent of individual confounding, and they mentioned some problems which were summarized under the term 'cross level bias' e.g. due to non-linear effects, effect modification and inhomogenous distribution within a given subarea.

In the following those fields of environment, which were the subject of more systematic research into MS by the ecological approach shall be discussed.

Relief characteristics

Regarding altitude, or mountain character of landscape, respectively, the literature is fairly inconsistent. In a large number of studies higher rates in more elevated regions in comparison with lowlands were emphasized (5–17) some of which included even a formal statistical analysis (8, 11, 14,

17). There are, however, a somewhat smaller number of negative investigations (18–25; unpublished data for Albania). Thus the problem remains controversial, but the direction of the results is clearly biased: either no difference or a higher risk in more elevated areas,and, with the exception of Cyprus (24), not the reverse, was reported. This might point to environmental features associated with mountains in some, but not in other regions, and thus actually facilitate the search for true risk factors.

Natural radiation

This is another point of interest, especially under the aspect of a biological plausibility, regarding its possible impact on immune function. There are surprisingly few investigations giving only sparse data so far. Thus Barlow, in 1960, performed an extensive correlation analysis between the MS mortality rate and cosmic ray intensity for which geomagnetic latitude was used as a proxy measure (26). He found such a correlation worldwide and within individual countries such as the USA, Australia, and Italy. Resch (27) recently revived this view, and confirmed Barlow's findings on the basis of more recent prevalence data on the global level. In addition he emphasized the parallels of MS and geomagnetic latitude in the most northern parts of Europe. Apart from sun radiation (*vide infra*) natural types of radiation were not studied further. For example an interesting question might be a role of terrestric radiation due to radon decay which is high in mountainous areas (28). This might be an important subject for future research by both the ecological and the case-control approach.

Climate

A classical comprehensive analysis was carried out by Acheson et al. in 1960 for the USA (29) where they clearly demonstrated a high correlation between MS mortality and both low temperature and low December solar irradiation, i.e. a lack of sunshine. This was later confirmed by Norman et al. (11) who found a positive association for a large number of climatic variables. Statistical adjustment for latitude removed, however, most of these associations, with the exception of a product term of rainfall and low temperature. The problem of such an adjustment will be treated below. In a greater number of further regions positive associations with MS were reported for low temperature (8, 14, 17, 18, 31–34). As far as humidity/ precipitation is concerned, our own investigations by the correlational approach in the USA (33), France

and Australia point in particular to the winter conditions as more important in that respect. For example in the USA, beside the consistent correlation with low temperature, a positive one with snowfall but not with annual rainfall was found. The same was true for winter, but not for annual and summer humidity in Australia (Table 1). In France the MS mortality (35) showed a very similar northeast-to-southwest gradient as both January temperature and January humidity (36) (Table 1). In the Australia and New-Zealand region MS prevalence data from the 1980's (37) showed a highly significant correlation with latitude but, using climatic tables (38), also with low annual temperature ($r_s=0.883$; $p<0.01$), low sunshine ($r_s=0.767$; $p<0.05$) and higher winter humidity ($r_s=0.929$; $p<0.02$), whereas non-aridity and the number of fog days were not significantly related. In contrast, in comparatively few studies no association with climate was found, most of which did not include a formal analysis (19, 21, 23). In Albania, a formal reanalysis did not demonstrate a correlation with climate (39) (Lauer; unpublished data).

When looking for a biological rationale for climatic influences in MS, a direct influence on immune functions (40) might be discussed. Another interpretation might claim an indirect role by more frequent respiratory tract infections (RTI) for which, among other features, both winter season and a cold, damp climate have been elaborated as risk factors (41). The neurotropism of coronaviruses, for example, which are the second most frequent class of viral agent in upper RTI (41, 42, 43), and the discussion of their etiological role in MS (44, 45), and the obvious slight neurotropism of further viruses causing the 'common cold' (e.g. rhinoviruses and parainfluenza viruses) as indicated by their initiating role in ADEM (46) shall be mentioned in that context. Such viruses might operate as blood brain barrier – damaging agents, leading to an inflammatory immunological reaction into the CNS as the target organ of a later chronic autoimmune process (47).

Geological features, water and soil

In a number of papers a possible role of special geological formations, geochemical factors or soil types was claimed. Often these considerations were based on map comparisons. Thus Layton et al. (48) emphasized the similarities between the distribution of MS and podzolic soils having a low molybdenium (Mo) outwash, resulting in higher soil concentrations of Mo. Warren et al. had suggested a possible role of high lead concentrations (49). A very extensive study was made by Irvine et al. in

Table 1. Studies demonstrating a positive ecological association between climate and the rate of MS. *: formal statistical comparison included. Marginal associations in brackets. (W): only winter. (+) marginal significance

First author	Region	Low temperature	Rain/Humidity	Others	Ref.
Acheson 1960*	USA	pos	no	lack of sunshine	29
Norman 1983*	USA	pos	neg	diverse	11
Mutlu 1960*	Turkey	pos	no	fog	18
Cernacek 1971*	W Slovakia	pos	pos	–	8
Kalafatova 1987*	Bulgaria	pos	(+)	lack of sunshine	30
Tjazkorob 1987	Ukraine	ng	pos	–	31
Yarosh 1988	NW Ukraine	pos	pos	–	32
Lauer 1989*	Hesse/Germany	pos	pos	–	14
Lauer 1994*	South Hesse	pos	pos	–	17
Lauer 1994*	USA	pos	pos(w)	–	33
Lauer 1994*	Europe/Mashriq	pos	pos	–	34
Lauer 1994*	former SU	pos	pos	–	34
Lauer unpubl.*	France	pos	pos(w)	–	–
Lauer unpubl.*	Australia	pos	pos(w)	lack of sunshine	–

the Henribourgh MS focus in Saskatchewan, Canada, were 8 cases in a population of less than 75 were found (50). In this comprehensive analysis they demonstrated, in comparison with control communities and North American standards, especially high soil concentrations of chromium and some other elements, and low concentrations of aluminium, borium, cobalt, manganese, molybdenium and others. Also in the drinking water a number of deviations were found, e.g. a high molybdenium content, in contrast to the soil. The lead concentration was fairly high in the soil, but low in the water. These data are, at first, difficult to interpret, but doubtless valuable for further research. Both neurochemical and geochemical knowledge is needed to generate plausible hypotheses on the basis of these observations.

In an ecological analysis of drinking water parameters in the German state of Baden-Württemberg (35 counties). We found a negative correlation between MS mortality with halogenated hydrocarbons and lead (25) thus confirming for the latter element the findings in Henribourgh, but clearly no deviation for chromium and selenium was demonstrated. A surprising and so far unique finding in that study was a significant positive correlation of MS with polyaromatic hydrocarbons (r_s=0.511; p=0.003) in the water. The source of this water contaminant was, at first, unclear, but burning of agricultural fields is one possible explanation.

In a small area comprising 11 subunits in Southern Germany a marginally significant correlation between the MS incidence and the proportion of clay soils in contrast to sandy soil types was found (17,52). In Finland (9 counties) a similar – albeit non-significant – trend was confirmed (r_s=0.450; n.s.), and map review of Denmark (53) indicated also a trend association with prevalence data ac-

cording to childhood residence elaborated by Hyllested (54).

Data from descriptive epidemiology point to a particularly high risk of MS in regions characterized by a large proportion of peat surface, e.g. Finland, Ireland and Scotland. In addition, local associations were reported in Northwestern Poland (55), in Northern Ireland (56) and parts of the former Soviet Union (57). Within Ireland a comparison of maps shows a close similarity between the distributions of both peat-bogs (58) and MS (59), and a formal analysis revealed an almost threefold MS risk in the counties above vs. below the median for peat production (OR=2.87; 95% CI 2.52–3.15; p<0.001). In addition a marginal correlation was found over all 26 counties (r_s=0.353; p<0.1). A similar correlation was present in Finland (r_s= 0.682; p<0.05), but not in the Netherlands or Denmark (data not shown).

Forestry

Whereas the association between MS and total forest remains equivocal, a more consistent correlation is evident for the more specific term 'coniferous forest' which was significantly correlated with MS in the whole European/Near East region (34), in the former Soviet Union (34), in Finland (r_s=0.655; p<0.05) and in the state of Hesse in Germany (14), in spite of various types of MS rate. In Norway such a correlation was found with the felling of coniferous wood (60) and with the percentage of conifers in all forest trees (Lauer; unpublished data). No such association was present in seven further countries, but a comparison of maps of the MS distribution in Romania (61), Czechia (15) and the former Yugoslavia (62,63) with special maps on forestry (64) revealed clear similarities in those 3 countries also. In addition,

a correlation between the MS rate and the proportion of conifers in local forests was found in 44 communities in a rural mountainous region in Germany (52). In that context some chemical features shared by coniferous wood and peat, e.g. a higher resin content (65) and a low content of lignin methoxy gropups (66), shall be mentioned, especially with respect to the use of both as a source of food additives (*vide infra*).

Industry

A very important question, especially in a time of increasing public awareness of environmental problems, is whether or not MS is more frequent in industrialized areas, and if emissions from industrial plants might play a contributory role in causation. This was claimed by Jedlicka for the Czech Republic were prevalence rates higher than 100 per 100,000 were found in the Northern Bohemian region which is characterized by heavy industry, especially from the chemical and metal processing sectors (15). He also drew special attention to the air contamination with sulfodioxide which is a classical indicator of heavy industrial activity, but also with nitroxides originating from motor vehicles. Ecological studies on that subject have not been done elsewhere, but are highly suggested wherever exact measurements are available. A similar accumulation of MS cases in industrial regions was also reported in Hungary (67).

Using published data, we had looked for such an association on a broader range of countries where manufacturing was expressed in terms of employees by populations (14, 17, 22, 25, 33, 34, 52, 60; unpublished data for Australia and New Zealand). In about half the regions under study, i.e. in Switzerland, France, Norway, Finland, Southern Hesse, and the Europe/Near East region, a significant association at least on the 10% level, was found in spite of varying types of MS rates. The question arises whether this finding is due to confounding by social service parameters, for example by a more efficient social security system, or a stronger tendency to seek medical help in industrialized areas. Alternatively sociocultural features more closely related to the lifestyle in industrialized regions might be discussed. No definite answer can be given at present.

Industry as such is a very abstract term having 'grab bag' character, similar to latitude or socioeconomic status (SES). When looking at specific industries defined by a certain exposure pattern there was a much lower consistency for the chemical and plastics industry, for which a correlation was found in France (22) and over the whole range of Europe/Near East (34), and also within the

small area of Southern Hesse (17), but not in 8 further regions (14, 33, 60; unpublished data for Australia and New Zealand). Thus confounding appears a possible explanation. This might apply also to Northern Bohemia considering the above-mentioned similarities with defined geoclimatic features. An industry sector that was inductively found to be related to the MS risk was the paper industry. Surprisingly this variable was found to be significantly associated with the MS risk in 5 out of 12 regions, i.e. in Switzerland, Norway, Denmark, Australia and the Europe/Near East region (34, 68; unpublished data). A conceptual link with the geographical variable 'coniferous wood' shown before exists, since for economic reasons the paper industry which is mainly processing coniferous wood (69), is localised predominantly near its natural source.

Occupation

A possible occupational risk was addressed by numerous authors. The problem was studied in part using case-control studies, more often, however, by case-base approaches. Most of these studies did not meet the requirements of an optimal design; e.g. no age and sex adjustment was performed. On this background the inconsistent results must be seen. So far no clear association with a higher SES was demonstrated, but the direction of results is clearly biased in favour of a higher SES (70, 71). However, detection bias must be seriously considered. When looking at single occupations the claimed association with shoe and leather work in 2 Italian studies in which organic solvents were discussed as a possible risk factor (72, 73), could be biased by misclassification of exposure, as addressed explicitly by Giuliani et al. (73). The problem of a higher risk due to organic solvents remains a matter of debate (74, 75), and the presently available data do not justify considering this exposure as causal. Regarding health – care workers, an association had been reported by Shepherd & Downie in North-east Scotland (76) and re-emphasized more recently (77). In contrast Dean & Gray (78), using mortality data for the UK, could not find such an association. We had addressed this question in analytical studies in the Darmstadt region of Germany. In comparison with the total state population we could not find any deviation from expectation for nurses (52). However, when the pattern of occupations during adolescence, i.e. at age 15–20, was analyzed in comparison with the population at that age in an appropriate time frame, a surprisingly high risk was found for nursing ($OR_{MH} = 5.60$; 95% CI 2.99–10.47; $p < 0.00001$), but not for other health-care

providers (e.g. physicians and their assistants). Further questioning of the nurses forming this group clearly revealed that exposure to clinically manifest MS patients at work did not play any role; such exposure was the exception (79). Either chemical influences at work or the particular physical strain to the cervical spine by lifting and twisting (80) in agreement with Poser's hypothesis on microtraumatization to the cervical cord (81), might be discussed (79).

Housing

For dwelling density, i.e. the number of persons per room, a negative association was found in the USA for Kurtzke's case control ratio (33) and earlier by Swingler and Compston (82) in 64 communities in Wales. In contrast, I found a positive, but non-significant association for the MS mortality in 2 German areas (14, 17). In the former two regions a clear association with a high SES has given rise to substantial confounding, and the role of dwelling density per se remains questionable. This also applies to higher sanitation for which a positive association was found in the USA (33), but not in 3 German areas (14, 17, 25). Thus Poskanzer's hypothesis on a protective effect of poor sanitation (83) is not strongly supported by these ecological data and by case-control studies (52, 84–87).

Religion

Religious affiliation with its strong impact on lifestyle might be an important indicator for true risks, as broadly discussed in cancer research (88). An absence of MS was reported for the Hutterite community in Southern Canada (89), which follow a medieval lifestyle in many respects, but are non-vegetarians (90). A possible role of alcohol and tobacco is contradicted by the non-deviating risk among Mormons forming the population of Utah, USA (91). Regarding the distribution of MS in the European/Near East area (34) and also in the former Soviet Union as reported by Boiko (57) the rates appear clearly higher in countries belonging to the Christian tradition in contrast to the Islamic world. This was actually confirmed by a systematic statistical analysis for both areas (34). A formal comparative analysis of MS prevalence in Albania (92) and Macedonia (16) and maps showing religious affiliation (93,94) revealed a marginally significant association with the Christian culture, too, in both regions (chi^2=5.50; d.f. 1; p<0.1; and chi^2=4.79; d.f.2; p<0.1, respectively). Regarding a possible asociation with meat (*vide infra*) studies among the Seventh-Day Adventists might be of paramount interest.

Diet

In this field four topics have been studied more systematically. Poskanzer had described in a case-control study on the Orkneys and Shetlands that patients had more frequently consumed a special local dish containing animal brain ('potted head') (86). I made an attempt to confirm this association in a non-matched design where I investigated 100 cases versus 91 controls. Both groups were comparable with respect to age and sex distribution. No difference could be found for 'brain ingestion' (OR=1.86; 95% CI 0.86–1.34; n.s.). A special type of sausage frequently containing brain material (so called 'yellow sausage' because of its bright yellow skin) was even less frequently reported by cases than control (OR=0.47; 95% CI 0.23–0.97; p= 0.04), and 'either or both' showed no difference (OR=0.73; 95% CI 0.40–1.34; n.s.). Thus Poskanzer's findings could not be confirmed.

'Animal fat'was first reported as a putative risk factor by Swank et al. in their famous study in Norway (5). They found higher MS rates in meat – consuming areas, but also 'butterfat' showed a remarkable geographical association with the incidence. Subsequent ecological studies did not reveal a clear distinction between 'total fat' and 'animal fat' with respect to the MS association (95–97). In contrast, the majority of case-control investigations confirmed the animal-fat hypothesis by finding increased odds ratios (52, 98–101), especially when childhood was considered and 'butter' was the focus. The biological rationale of this variable has been broadly discussed, and influences on both membrane composition of myelin and inflammatory mediators such as prostaglandins and leukotriens are still a matter of discussion (102).

For dairy food a higher consistency was revealed by ecological studies; especially when consumption data were used, a significant relationship was found throughout (33, 34, 96, 97, 103). In 4 further countries I could not find a within-country covariation between MS and milk production (60; unpublished data for Albania), but this proxy measure might be less appropriate. Case-control studies revealed inconsistent results, even when childhood was focused on in the analysis. This pertains also to the special variable 'unpasteurized milk', for which 2 studies found an increased (98, 99) and 2 others an equal (52, 86) risk in both groups. In spite of these inconsistencies and although confounding might explain the ecological associations (*vide infra*) this feature warrants further investigation, all the more since a biological plausibility via animal viruses (e.g. retroviruses) or allergic mechanism cannot be debated; on the

other hand first serological data on retroviruses did not lend support (104).

When looking at meat consumption there is a fairly high consistency, but again predominantly so in extended areas like the USA, the European/Near East region and Australia (Table 2). In these areas more reliable consumption data were at hand. Where the crude proxy marker 'density of butchers' was used no such clear-cut association was found. A similar association with meat consumption was reported on the global level (95, 96, 97, 105) and in Norway (5). Confounding might, however, play a role at least in these studies covering a large territory. The majority of case-control investigations (84, 85, 98, 99, 106, 107) did not find an increased risk due to meat intake which was, however, analyzed mostly either at the time shortly before onset or during total life-time before disease manifestation. The only study focusing on childhood exposure revealed an increased risk for the variable 'raw meat', in spite of likely overmatching in the study design (98).

Based originally on considerations on the MS epidemic in the Faroe Islands (108) I had proposed the hypothesis that a special type of meat, i.e. meat processed by nitrite and subsequent smoke-curing might play a role in the etiology of MS (109). It was based on and confirmed by ecological comparisons. For example in both France and Switzerland which show strong geographical variation in that respect, a correlation between both features was found (110), and in the Mediterranean/Near East region the association was particularly obvious in form of a similar gradient between Italy and Malta (111). Finally the absence or rarity of MS in some populations (e.g. Asians, Eskimos, Lapps, Australian Aboriginals, Maori, American Indians, Bantu, Boers) would be in agreement with this hypothesis (47).

A preliminary interim analysis of a case-control study revealed a significantly elevated risk ratio for the variable 'saltpeter/nitrite use' in cases in which home slaughtering was performed during childhood (OR=3.5; 95% CI 1.6–7.8; p<0.02). There
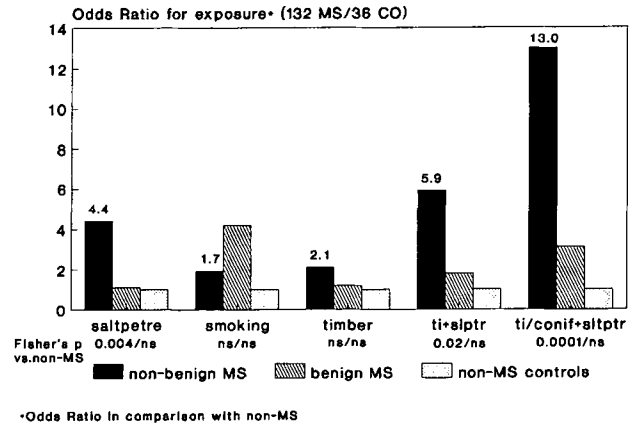

Fig. 1. Association between the risk of MS and some specific practices of meat preservation after home slaughtering during childhood. Preliminary results of non-matched case-control study. ti/conif: timber or coniferous fire wood used for smoke generation. 'benign' defined as in ref. 129.

was also a significant risk for the combination of saltpeter with timber obtained from a professional wood source in contrast to private fire wood (OR= 5.0; 95% CI 1.3–18.3; p<0.02) and – still higher – when coniferous fire wood was included as an additional alternative into that product term (OR= 9.5; 95% CI 2.6–35.1; p<0.0002). The rationale behind this combinatory term is that timber is in the vast majority coniferous in Europe in contrast to fire wood which originates mostly from broadleafy trees (112). The OR was especially high in the non-benign MS cases, whereas no real difference was found between benign MS and non-MS controls (Fig. 1). Methodological shortcomings in the study have been corrected and it is now ongoing. A very high odds ratio was found for the variable 'smoked pork' in a high-risk area of MS in North-West Croatia (99).

The hypothesis is also compatible with the temporal pattern of MS in the Faroe Islands, where the person-years at risk for the native Faroese MS patients at age 5–15 showed a large peak corresponding to the period when peat-smoking of meat was transitorily more common (109); this practice

Table 2. Our own ecological studies on meat consumption, or proxy measures, in relation to the rate of MS. P: prevalence; I: incidence; M: mortality; CCR: case-control ratio (Kurtzke et al. Neurology 1979: 27: 1228). MS data from published sources

	Region	N	MS	Exposure	r_s	P	Ref.
	USA	48	CCR	Meat sales	0.599	0.0001	33
	Europe/Mashriq (beef)	28	P	Meat intake	0.582	0.01	34
	Europe/Mashriq (pork)	28	P	Meat intake	0.639	0.001	34
	Australia	6	M	Meat sales	0.829	0.05	unpubl.
	Hesse	20	M	Butchers' density	0.545	0.05	14
	Baden-Württ.	35	M	Butchers' density	0.143	n.s.	25
	Denmark	20	P	Butchers' density	0.067	n.s.	unpubl.
	Switzerland	22	P	Butchers' density	0.239	n.s.	unpubl.

MS IN FAROE ISLANDS
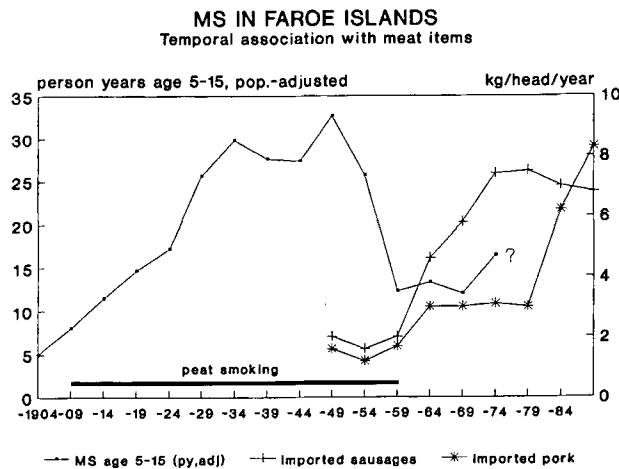Temporal association with meat items

Fig. 2. Temporal pattern of childhood-risk of later MS in comparison with selected nutritional items in the Faroe Islands. MS data from Kurtzke & Hyllested (108) and Kurtzke et al.(114). Meat import data from Danmarks Statistik. Period of presumable preservation by peat smoke reconstructed from refs. 109 and 113. ? indicates unknown further course of MS epidemic no. IV (114).

ended abruptly in the late 1950s (113). The most recent increase of the local MS risk (114) is lagging approximately 10 years behind a parallel increase of sausage imports, as revealed by a comparative evaluation of Faroese trade statistics (Fig. 2).

A biological rationale for this environmental variable is provided by a possible immunological hapten role of nitrophenol compounds occurring in this type of food (115, 116). Both coniferous wood smoke and peat smoke have a higher likelihood of generating such compounds due to their lower methoxy-group content (66, 117) (allowing nitro-group addition) and the additional formation of nitrosated polyaromatic hydrocarbons (118). Such nitrophenolic compounds are of particular interest in the context of autoimmunity, because they are prominent target antigens and thus possible stimulators of the natural immune system, perturbations of which are now considered of importance in the generation of autoimmune disorders (review in ref. 47). Most interestingly, both molecular mimicry between nitrophenols and MBP on the level of natural antibodies (119), and the intrathecal synthesis of such cross-reacting natural antibodies in MS patients (120) have been demonstrated. The amphipathic character of the hapten with its predominating aromatic ring structure appears of paramount interest as a basis of cross-reactivity with respect to a strongly hydrophobic epitope around amino acid 90 in MBP. Several studies suggested a more specific immune response in HLA-DR2 positive MS patients towards this particular epitope (121–123). As a possible alternative, drugs cross-reacting with nitrophenols

like tetracyclines, polymyxine, phenothiazines and salicylates (124), when applied during childhood, might be discussed in part of cases, and should be studied, as dietary nitrophenols, by a proper epidemiological design. These considerations were outlined elsewhere (47).

Agriculture

Several hypotheses on the role of agricultural features were formulated. For example Shatin claimed, on the basis of distributional similarities, that gluten from wheat might play a role in the etiology of MS (125). We have included this variable in ecological studies in 11 areas so far, and in only one (Norway) a significant correlation could be found. This is at variance with oats for which a consistent correlation with the rate of MS existed in 10 of 13 regions (Table 3). When looking for a biological plausibility, food antigens, immunostimulating lectins and plant pathogens might be discussed; the hypothesis by Palo & Wikström on a possible role of oat sterile-dwarf mosaic virus (126) shall be mentioned in that context.

The topic 'oats' was the subject of our own case-control study covering childhood at age 5–15 in 427 MS patients and 103 controls. No significant association was found (OR=1.29; 95% CI 0.84–1.91; n.s.). Thus the consistent ecological association is rather more prone to confounding, but as such it may point to highly and consistently MS-associated unknown variables. The fact that it applies to a plant showing complex geoclimatic small-scale dependencies (e.g. on local soil, climate, etc) leads to the suspicion that an important MS-related agent or its vector(s) might have the same basic characteristics, i.e. be related to the plant kingdom. Some natural features showing such similarities were mentioned above.

There were several claims on a role of animals,

Table 3. Correlation (r$_s$) between MS rate and extent of oats cultivation (in % of arable land or cropland). Further legend see Table 2

Country	MS rate	r$_s$	P	Ref.
Denmark	P	0.450	0.05	60
Switzerland	P	0.639	0.01	60
France	M	0.476	0.05	22
Sweden	P	0.432	0.05	unpubl.
USA	CCR	0.370	0.01	33
Australia	M	0.886	0.05	unpubl.
New Zealand	M	0.929	0.05	unpubl.
Hesse	M	0.561	0.10	14
Baden-Württemberg	M	0.334	0.10	14
Southern Hesse	I	0.536	0.10	17
Norway	M	0.186	n.s.	60
Finland	P	0.000	n.s.	60
Netherlands	P	-0.495	n.s.	60

especially as vectors of putative viral agents. Generally, only farm animals can be studied by the ecological approach. The evidence is actually very weak. For cattle such an association was shown on a global scale (127), but within single countries I could find it only in 3 out of 14 (Norway and 2 German areas, the latter with borderline significance) (14, 17, 22, 25, 33, 52, 60; unpublished data for Albania). Sheep and goats showed very conflicting results including highly negative associations in France (22), Norway (60) and Switzerland (60). Overall this is in agreement with studies by Malosse et al. (127), who did not find a correlation with any house pet either. Kurtzke & Priester (128) could not demonstrate any correlation between dog-bite and canine distemper frequency, and the MS case-control ratio in the USA. Most case-control studies on animal exposure were negative, although a number of positive reports were published for dogs (see Cook, this volume).

Multivariate analyses

Multicollinearity and, thus, confounding is an important problem in ecological studies, especially those in large territories like the USA, the former Soviet Union, Canada and Australia.

In the USA I had found a univariate correlation of Kurtzke's case control ratio (91) with a great number of exogenous variables from both the geoclimatic and the sociocultural compartment, including latitude, low temperature, sales of meat and dairy products, and low sales of fruit and vegetables and of fish. In addition, good sanitation, oat cultivation (33) and also low dwelling density were correlated with the MS risk.

An appropriate approach to disentangle such a multicollinear system can be factor analysis which was applied to the U.S. data (33). Interestingly, two independent factors could be identified, one of which is mainly characterized in sociocultural and the other in geoclimatic terms. The first bundle includes indicators of higher affluence like good sanitation, high meat consumption, low housing density, and a higher intellectual level as indicated by the printing and publishing industries. The other one was a geoclimatic bundle characterized by latitude and low temperature, but also by a low consumption of fish and fruit/vegetables, a high consumption of dairy products and oat cultivation. When applying factor analysis to the European/Near East region, using recently published prevalence ratios from 28 countries, again two MS-occupied bundles could be identified (34). The first one was characterized by geoclimatic variables, including 'cow milk consumption', as in the US. The sociocultural bundle included variables as 'Indoeu-

ropean ancestry', 'Christian tradition' and dietary factors like 'pork' and 'smoked meat'. Interestingly health care and higher SES formed a separate bundle which was, however, not related to MS, and thus cannot sufficiently explain its variance (34). A further region showing a similar dichotomy of variable bundles was the state of Hesse in Germany. Here again an independent association of the MS rate with the geoclimatic *factor* including low temperature, high precipitation and altitude along with some others, and with the variable 'butcher's density'as a proxy measure of meat consumption, was found (14).

An alternative approach is stepwise multiple regression analysis which was applied to the U.S. data. In backward elimination, when latitude was included in the model, only this variable ($p < 0.0001$) and dairy food in addition ($p = 0.002$) made an independent contribution to the variance of MS. When latitude was excluded, however, 'meat' ($p = 0.0003$), 'dairy food' ($p = 0.0003$) and 'low temperature' ($p < 0.0001$) were independently associated with the risk of disease, the latter making the highest contribution (adjusted $R^2 = 0.676$; $F = 33.76$; d.f. 3, 44; $p < 0.00001$ for this model). Thus, also by this technique, a certain dichotomy between 'climate' on one hand and 'meat' on the other is suggested with respect to the MS association.

Conclusions

On the basis of univariate and multivariate ecological analyses on MS with special emphasis on consistent associations, the following conclusions can be drawn: there is a highly consistent ecological association between different types of MS rates and 'low temperature'. Regarding other climatic features, the correlation with 'humidity' or 'precipitation' is more equivocal, but a much better fit is reached when only winter conditions are regarded. Similar climatic influences were reported for nonspecific respiratory tract infections, through which climatic factors might be operating. There is also a rather consistent and even individual-based association with 'animal fat', but bias and confounding cannot be excluded in view of the rather good knowledge of MS patients of the underlying hypothesis.

There are more equivocal associations which should be tested further with 'mountainous landscape' or 'altitude', with 'peat soil', especially in some high risk areas, with the occurrence of conifers, and also with 'industry' as a whole, but not with the chemical/plastics industry. The more consistent association with paper industry might be due to confounding, but deserves further atten-

tion. Meat consumption is also more consistently associated with the risk in ecological terms, as is dairy food consumption.

There is no consistent association with any farm animal; thus hypotheses on a possible transmission of viral agents from these animals to man are not strongly supported. There is no consistent occupational risk; the organic-solvent hypothesis remains highly controversial. The role of nursing appears unclear, but based on our own data, occupational transmission is not a likely mechanism. Environmental risks *sensu strictu* in form of emissions from industries and motor vehicles, and different types of natural radiation were insufficiently studied so far. Finally, multivariate testing points to a possible interaction of both geoclimatic and sociocultural features in the exogenous etiology of MS, where climate on one hand and dietary factors from the broader complex of "mammalian meat" on the other, appear as outstanding features.

Acknowledgements

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