Section of Pathology

President G Dick MD

Meeting 21 October 1975

President's Address
[Abridged]

The Etiology of Multiple Sclerosis

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Multiple sclerosis (MS) is a disease which presents problems to the morbid anatomist, the histopathologist, the chemical pathologist, microbiologist, immunologist and to the clinician; it is a problem in which I have been interested for many years and in which I am still actively engaged. It is a disease which is disseminated in time and space, manifested by separate episodes of double vision, nystagmus, numbness, weakness, ataxia, speech difficulty, tremor, precipitancy of micturition or other symptoms. The disease has a tendency to remission and relapse and may progress or remain stationary over the years.

The pathology is characterized by patches of demyelination scattered throughout the central nervous system which in the later stages undergo gliosis. The earliest lesions seem to be represented by the penetration of lymphocytes from the blood stream into the brain.

There is at present no diagnostic test, but the majority of patients have an increased level of IgG in the CSF and the presence of oligoclonal bands supports the diagnosis, but there is nothing truly pathognomonic in the CSF findings.

The diagnosis is a clinical one which is not easy in the early stages but recently 'evoked potential' techniques which provide evidence of delayed conduction have been introduced and these should aid early diagnosis.

In trying to solve the etiology of any disease we must follow the scientific method of establishing the data and then making a hypothesis which can be subsequently tested by treatment or preventive measures. It is first necessary to establish time, place and person: Among whom does the disease occur? Where does the disease occur? When does the disease occur? Having answered these questions we can then ask why it should occur.

Among Whom?

MS is one of the commonest causes of crippling of adults and is probably the commonest disease of the central nervous system in adults of 20 to 50 years. The age of onset peaks at about 30–40 years and is slightly earlier in females than in males; the prevalence in females is not influenced by marriage.

It has been suggested that the disease is commoner in the upper socio-economic group but I think this may merely represent the fact that people in Social Classes I and II may more readily report such symptoms as transient diplopia or paræsthesia or heaviness of a limb than might patients in Classes IV and V.

Genetic factors: Although 10% of MS patients have another member of their family affected, the disease is not hereditary but it is familial. Recent surveys have shown that patients with MS have higher frequencies of some of the histocompatibility genes than have controls, e.g. the relative risk of having MS seems to be about seven times times greater in individuals who carry the HLA (human leukocyte antigen) B7 determinant than in those who do not. Furthermore, once the disease has developed such patients show an increased rate of progression. Although cases tend to occur among family members who carry the LD-7A determinant nevertheless many family members who do not have MS carry this determinant.

Where?
Though the disease is nearly worldwide there are areas of high prevalence with rates of up to about 60 per 100 000 which are to be compared with rates of low prevalence of 5 per 100 000.

The disease is more prevalent in the northern hemisphere and the rate increases from the Equator up to about 60°N and is at its maximum between 40° and 60°N. The prevalence of the disease also increases from the Equator south, but this is not so obvious as north of the Equator, for the disease is in general much less prevalent in the southern hemisphere. The gradation associated with latitude is particularly well seen in studies which have been done in North America. The prevalence in Winnipeg or Halifax is about 3 or 4 times that of Charleston (South Carolina) or of New Orleans. The influence of latitude on prevalence is also clearly demonstrated in studies on the west coast of North America and does not seem to be related to medical care or ascertainment.

This latitude factor seems to be related to place of birth and has been thought to be due to some environmental factor; while this may be so, the prevalence data will have to be looked at again in the light of recent work on the histocompatibility genes. The high prevalence of the disease in Scottish and Scandinavian peoples may be related to the frequency of HLA-A3 and HLA B7 histocompatibility linked determinants. Conversely these determinants are rare in Japanese and Bantu people among whom the disease is of low prevalence.

It is of interest that if people emigrate from a high risk to a low risk area, e.g. from Europe to the Middle East or from England to South Africa, they seem to take their risk with them. It will be of considerable interest to see what happens in the case of immigrants from the West Indies and Africa (areas of low risks) who have become resident in the UK and other parts of Europe in recent years.

While there seems to be an environmental factor 'responsible' for the geographical distribution of the disease, this nevertheless may be primarily determined genetically.

When?
There is no evidence that the disease occurs in epidemics. Some have suggested that the onset may be associated with a febrile illness, while others say that patients with MS have fewer incidental respiratory and gastrointestinal upsets than other people. A transient neurological illness in childhood which has been associated with the later development of MS in some studies could represent not an 'associated' disease but, as I shall discuss later, the first episode of the illness.

Why?
Having established time, place and person, we are now in a position to ask why and what is the cause of this disease.

It seems clear that there is an important genetic factor as evidenced by the recent genetic studies and also from earlier epidemiological studies which have shown, for example, that 10% of MS patients have a relative affected and such observations as those showing that monozygotic twins have twice the risk of the disease as dizygotic pairs.

It is not an inherited disease and there is no significant genetic linkage but there does appear to be a selective vulnerability of persons who carry certain specific genes.

If there is a genetically determined soil – what is the seed? As I mentioned, the geographical distribution suggests that there are environmental factors at work which of course may be genetically determined.

Since at least 4% of patients with MS have affected parents or siblings, it has been suggested that there must be some common exposure. If there is such a common exposure it is suggested that this occurs many years before the onset of the disease as evidenced by such observations as the risk of MS in both members of a marriage which is similar to what would occur by chance in the general population. This suggests that if there is a common environmental factor it must act before marriage. A number of studies have been done on the time of onset of the disease in individuals who have been brought up together which have suggested that if there is a common exposure MS has a very long incubation period with a minimum of 12 and a maximum of 40 years in one study. It has been suggested that the age of common exposure is generally in childhood. The trouble with most of these data is that it is very difficult to define exactly the time of onset of the disease. There could be numerous subclinical or unidentified episodes before definite symptoms appear because of the extent of damage required to produce symptoms. For example, in the case of experimental poliomyelitis, some monkeys may lose up to 90% of anterior horn cells before paralysis is obvious. As mentioned, a transient paræsthesia of a limb or one side of the face, or weakness or heaviness of a limb, or dimness of vision could occur in a child

and never be observed or documented and could represent the onset of the disease. Data on time of onset, &c., should become more reliable with greater appreciation of the symptomatology and when the newer techniques providing evidence of delayed conduction, e.g. of the optic nerve (visual evoked potentials) or of sensory pathways (somatosensory evoked potentials), are more widely used.

The environmental factor: If there is common exposure to something associated with the environment (which may well be genetically determined), what could it be?

There seems to be no close relationship between the distribution of MS and various climatic factors such as sunshine, rainfall or temperature, or with geographical factors such as trace elements. But what else is geographically distributed? Obviously if one is trying to demonstrate a correlation between the prevalence of MS and some geographical or latitude factor there must be some *a priori* case for making the hypothesis. Because of the nature of myelin and its metabolism it has been suggested that fat in the diet might come into the picture and this is the hypothesis I wish to pursue.

Fatty acids: It seems that the geographical distribution of MS is related to the consumption of animal fats which are deficient in unsaturated fatty acids. Thus the disease is common in Western Europe and North America, where the consumption of animal fat is high; and uncommon in Asia, Southern Europe, Black Africa and Japan, where the consumption of animal fat has tended to be low. In advanced countries not only is much animal fat consumed but also large quantities of dairy products are taken in the diet and there has been a suggestion that the intake of dairy fat *per se* correlates with MS mortality. It has further been suggested that the geographical predisposing factor which accounts for the prevalence of MS might exert itself via cows' milk taken during infancy.

The two families of essential fatty acids which man seems to require in his diet are linoleic and linolenic acid and it is said that these fatty acids are destroyed by rumen bacteria and are virtually absent from cows' milk. Could it be that dairy products (and meat) from cattle provide a reduced amount of certain polyunsaturated acids in the diet which are necessary for the metabolism of myelin or alternatively that the intake of large quantities of fatty acids from animal and dairy products reduces the amount of essential fatty acids which are absorbed? Lack of these essential unsaturated fatty acids could lead to 'deficient' myelin. Alternatively it has been suggested that transfatty acids which are present in cows' milk might be damaging to the myelin of babies nurtured on cows' milk.

But what is the other side of the coin? There appears to be a negative correlation between the geographical distribution of MS and that of breast feeding; areas where breast feeding is common are also associated with a low intake of animal fats. But could it be possible that breast feeding is associated with the development of normal myelin which is not vulnerable to the initiating trauma of MS (whatever it is), while those fed on cows' milk have an inferior type of myelin which is susceptible to damage? This I am going to try and find out.

If diet in infancy has any effect on the vulnerability of myelin in MS, one has to assume that if the initiating trauma does not also occur in infancy then the myelin laid down in infancy influences the stability of adult myelin. It is of course possible that the initiating trauma does occur in infancy.

It appears that the 'brain spurt' in man is rapid till about the end of the first year of life and then continues, but at a slower rate, into early childhood. Is it reasonable to assume that the diet in infancy could markedly influence myelin lipid stability? There is good evidence to suggest that the degradation of most brain lipids is slow and as the brain is able to re-utilize some of them, at least some of what is laid down in infancy is presumably recycled. But quite apart from recycling, 'insufficient' nutrition with the wrong types of fatty acids which could result from the lack of mother's milk, could produce 'defective' myelin which is susceptible to trauma.

Experimental allergic encephalitis (EAE) is a demyelinating condition which can be produced by 'shocking' animals which have been sensitized to CNS antigens. It was shown many years ago that deficiency in certain essential fatty acids in the diet of baby rats renders them more susceptible to EAE. This observation becomes even more interesting now that a relapsing model of EAE has been reported which makes this condition very like MS. So if the experimental disease can be influenced by the fatty acids fed in infancy why not also the natural disease (MS)?

The initiating trauma: Many agents have been suggested, bacteria including spirochætes, rickettsia, mycoplasma and viruses. There is no good evidence to implicate any particular infective

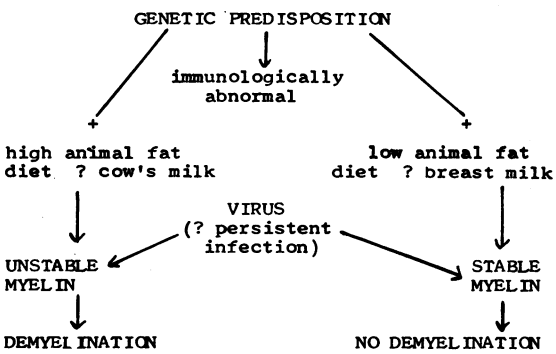

Fig 1 *Various factors which might be involved in the etiology of multiple sclerosis*

agent, but as a virologist I am most interested in a possible viral etiology. I first became interested in this many years ago (1958) when the Russians claimed to have discovered the virus of MS which we showed to be rabies virus – but that is another story!

I do not think that the agents producing the slow virus infections such as scrapie, Creutzfeldt-Jakob disease, kuru or mink encephalopathy bear any resemblance or relation to the hypothetical agent triggering off MS. These slow virus diseases are progressive, non-remitting, relentless, degenerative fatal diseases with spongiform encephalopathy quite unlike the picture of MS. Confusion of these diseases with MS has, I believe, muddled much of the thinking about the etiology of MS for years.

What evidence is there that there might be a viral etiology? No one has found any other infective agent, and it is suggested from the raised levels of IgG in the CSF of a large proportion of patients and from observations that several viruses can 'go to sleep' in the CNS and be 'wakened up' by various stimuli. It is known that this occurs with measles in the case of subacute sclerosing panencephalitis (SSPE) in which disease the virus lies latent in the CNS for six or seven or more years, or with zoster in which varicella may remain latent for forty or fifty years. And there is the virus of herpes simplex which I believe goes to sleep in nervous tissue and can be awakened by the type of stimulus which may initiate a relapse of MS, such as pregnancy, infections, trauma or pyrexia. There is no evidence to suggest that herpes simplex virus is an initiating virus in MS but it would fit the role beautifully.

The idea that measles virus might be involved in the etiology of MS received a boost when it was found that the sera of MS patients had increased levels of measles antibody compared with matched controls. It was subsequently found that siblings of MS patients, particularly the female ones, also seem to have increased levels of measles antibody in their sera. It was also found that some patients with MS had specific measles antibody in their CSFs, but I do not think there is any good evidence to show that the specific measles antibody in the CSF is more than a spill-over from the serum. I shall not here discuss CSF: serum immunoglobulin and albumin ratios, but there is no evidence of replication of measles virus in the CNS as there is in SSPE.

The initiating agent of MS could be measles virus but it could be another virus or viruses. It could be a virus which goes to sleep and wakes up and produces damage which might stimulate an autoimmune reaction. It could be due to repeated attacks of several different viruses to which 'vulnerable' myelin is susceptible. It could be due to an infective agent or agents other than viruses.

A Possible Etiology

In Fig 1, I have tried to put together the various factors which may be involved in the etiology of this disease. I realize that Occam would have treated my proposed etiology very severely with his razor!

It is vain to do more
which can be done with less (Occam, 1290–1349)

However, it seems that MS patients may be genetically and immunologically different people. There is some evidence in some studies of immune deviation in some of them, but this awaits confirmation. Genetic types inhabit certain areas and have certain feeding habits. I have suggested that perhaps babies fed on maternal milk have 'normal' myelin while those fed on cows' milk have 'abnormal' myelin. All sorts of traumata might cause demyelination of abnormal myelin whereas normal myelin would be resistant.

The cause of MS is not yet known. I have tried to present the basic data which I consider to be 'dinkum' and to suggest one possible explanation that we are going to test.

ADDENDUM

A recent leader in the *Lancet* (1976, i, 459) lapped up by the media on both sides of the Atlantic made great claims for some observations made by Carp and his colleagues and by Henle and his colleagues. The *Lancet* really went overboard and made claims which went beyond those of the American scientists (Carp *et al.*, 1972, *Journal of Experimental Medicine* **136**, 618; Henle *et al.*, 1975, *Infection and Immunity* **12**, 1367; Koldovsky *et al.*, 1975, *Infection and Immunity* **12**, 1355).

Briefly it was claimed that when mice (and some other animals) were injected with specimens from

MS patients there was a depression in the count of the polymorphonuclear cells (PMN) of these animals.

In reviewing the reports the *Lancet* said: 'The essence of science is reproducibility.' The real problem of the PMN test is that it does not seem to be reproducible in the laboratory of origin and has not been confirmed by several other workers. For demonstration of this PMN depression, mice have to be uniformly healthy and there is variation in the results when different sexes and different strains of mice are used. Koldovsky *et al.* stated that because of this a number of experiments 'could not be evaluated because of gross variations in the control groups' and 'scheduled tests were cancelled because of the unhealthy appearance of the available mice'. What a test! 'Yet, satisfactory results were obtained in many tests.' It would have been wise to do the tests 'blind' with such a variable test system.

It was further claimed that this agent was neutralized by certain human sera: indeed there was no significant differences in the proportion of sera from patients, their relatives or their nurses which 'neutralized' the agent. With this type of result the possibility of a nonspecific neutralizing substance might have to be considered. The results are a long way away, in my opinion, from being acceptable as evidence of infection with the so-called MS agent, whatever 'it' is. Koldovsky *et al.* report that the role of the agent 'remains to be determined'. The *Lancet* claimed the 'findings seem to remove multiple sclerosis from the group of diseases of unknown ætiology and place it squarely in the sector of infectious diseases'. Time will tell – the MS field is full of unsubstantiated claims for causative agents. The *Lancet* considers the American work as 'an important milestone in multiple-sclerosis research'. So be it.

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Meeting 3 February 1976

A laboratory meeting was held at The Mathilda and Terence Kennedy Institute of Rheumatology, Hammersmith, London W6. Demonstrations were given.

Meeting 8 October 1974

Professor J W Stewart (*Middlesex Hospital, London W1*) delivered his Presidential Address which was entitled **The Coagulation Defect of Amniotic Fluid Embolism.**

Meeting 3 April 1975
with the Section of Urology
and the Medical Society for the
Study of Venereal Diseases

Papers were read on **Non-specific Urethritis,** as follows:

Chlamydia as a Cause of 'Non-specific' Genital Infection
Dr Eric Dunlop
(*London Hospital, London E1 1BB*)

REFERENCES
Dunlop E M C
(1974) In: Tenth Symposium on Advanced Medicine. Ed. J G G Ledingham. Pitman Medical, London; p 409
(1975) In: Recent Advances in Sexually Transmitted Diseases. Ed. R S Morton & J W Harris. Churchill-Livingstone, Edinburgh; p 275

Virology
Dr S Darougar
(*Institute of Ophthalmology, London WC1*)

Bacteriology
Dr D Taylor-Robinson
(*Clinical Research Centre, Northwick Park, Harrow, Middlesex*)

Papers were read on **Chronic Prostatitis,** as follows:

Prostatitis
Dr J K Oates
(*Westminster Hospital, London SW1P 2AP*)

Study of Prostatic Disease by Human Prostatic Fluid Samples
Dr D S Reeves
(*Southmead General Hospital, Westbury-on-Trym, Bristol, BS10 5NB*)

The Place of Bacteriological Localization Techniques in the Diagnosis and Management of Chronic Prostatitis
Dr Susannah Eykyn
(*St Thomas' Hospital, London SE1*)

Chronic Prostatitis. Perspectives of Occurrence: Morphological and Functional Factors in Chronicity
Surgeon Captain N J Blacklock RN

REFERENCE
Blacklock N J
(1975) *Proceedings of the Royal Society of Medicine* **68**, 505–508