Second Edition

McAlpine's
MULTIPLE
SCLEROSIS

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This account of the methods used and problems encountered in carrying out epidemiological studies of multiple sclerosis is intended to encourage caution in the interpretation of results. Examples like that of the Orkneys, where prevalence increased threefold over a period of 30 years despite stable or declining incidence rates, or Southern Italy and Sicily, where multiple sclerosis was considered rare until intensive surveys of small communities were carried out, should be borne in mind by anyone tempted to put much weight on the results of a single study. But there is no need to take too negative a view; many of the features of the epidemiology of multiple sclerosis have now been confirmed by different investigators, using a variety of methods. One may be confident that the unusual pattern of the disease contains important clues about its cause.

THE PATTERN OF MULTIPLE SCLEROSIS IN POPULATIONS

Sex

Population surveys consistently show that multiple sclerosis is more common in women than in men. By averaging data from 14 well-conducted prevalence surveys carried out before 1977, Acheson calculated that the risk for women was 1.4 times greater than that for men.[26] The results of several investigations carried out since suggest that this may be an underestimate; recently reported values for the sex ratio range between 1.9 and 3.1.[24,27-29]

Because these ratios are based on prevalence data, the possibility exists, at least in theory, that they may have been affected by differential survival between the sexes. Known differences in duration of disease or mortality between men and women are not great enough to account for a sex ratio of this magnitude and the surveys of incidence that give rates for the sexes separately confirm that incidence in women is consistently higher than in men. It is reasonable to conclude that women are about twice as likely to develop the disease as men.

Differences between the sexes in the incidence of disease occur very commonly and, even when the differences are large, they often fail to provide any strong clues about aetiology. It is possible that the higher incidence of multiple sclerosis in women reflects a hormonal factor that increases susceptibility, but there are many other, equally probable, explanations.

Age

The pattern of age of onset of multiple sclerosis established in early studies remains unchallenged by recent work. Onset of the disease is rare before puberty, but subsequently the incidence increases rapidly to reach a peak around the age of 30 years. It remains high in the fourth decade but then declines steeply. After the age of 60 years, the incidence is negligible. In the majority of surveys, the average age of onset of multiple sclerosis is slightly lower in women than in men. The difference is rarely more than 2 years and often much less. A difference of this magnitude could easily be the result of a systematic bias as might arise, for instance, if women tended to seek medical advice earlier in the course of an illness than men or if neurologists, aware that multiple sclerosis is more common in women than men, were inclined to make the diagnosis more readily in women.

A remarkable feature of the age-specific incidence curve for multiple sclerosis is that its shape does not vary with the underlying frequency of disease. In an American study, identical methods were used to survey populations in Seattle and Los Angeles.[30,31] The prevalence of multiple sclerosis in Seattle was more than twice that in Los Angeles, but the average age of onset of the disease and shape of the age-specific incidence curve showed little difference between the cities. The same phenomenon has been found in a recent survey of three towns in Australia.[24] The incidence of multiple sclerosis in Perth, W A; Newcastle, Queensland; and Hobart, Tasmania was measured over the period 1971–1981. There was a nearly threefold difference in incidence rates, but again, the shape of the age-specific incidence curves of the individual towns was similar. The observation holds true in the most extreme cases; the age-specific incidence curve for multiple sclerosis in Japan, where the overall prevalence is only about 2 per 100 000 population, can be made to coincide with that of Denmark, where the prevalence is

between the zones have no special significance and there is no reason to suppose any sudden discontinuity in the risk of multiple sclerosis between zones

Europe

The prevalence of multiple sclerosis is high over the whole of the northern part of Europe. The highest rates of all have been reported from the Orkneys, a group of small islands situated to the north of the Scottish mainland, where the prevalence in 1974 exceeded 250 per 100 000 population.[3] The prevalence is also very high in other parts of the United Kingdom. The frequency of the disease exceeds 100 per 100 000 population in the Shetland Islands,[43] in north east Scotland[29] and south east Wales.[44] In all of the five other regions of the United Kingdom that have been surveyed in the last 25 years or so, the prevalence is at least 80 per 100 000 population.[45-50]

Most reports indicate that rates of the disease are generally slightly lower in Scandinavian countries than in the United Kingdom. Surveys in Norway and Finland in the 1950s and 1960s found rates of less than 30 per 100 000 population, but recent work shows that the prevalence is now considerably higher. Conclusive evidence that the increase in prevalence indicates a rising incidence of disease is lacking and the rise may be partly or even wholly explained by improvements in case ascertainment and in the longer survival of cases. Within the countries of Scandinavia there are significant differences in the prevalence of multiple sclerosis. The methodology of the two most recent studies from Norway is comparable and the results show that the rate of disease is lower in the far north of the country (32 per 100 000 pop.) than it is in the south west (60 per 100 000 pop.).[51,52] In Finland, the prevalence is significantly higher in the rural western part of the country (93 per 100 000 pop.) than in the industrial south (53 per 100 000 pop.)[53] A recent study examined the incidence of disease in these two areas and confirmed that this is a genuine difference in the rate of occurrence of disease.[54]

The prevalence of multiple sclerosis in Germany and the Netherlands is similar to that found in Scandinavian countries. The most recent survey was carried out in the state of Hesse in West Germany where an overall prevalence of 58 per 100 000 for clinically definite and probable cases was reported.[55]

Reliable information about the frequency of multiple sclerosis in the countries of Eastern Europe is meagre and no new data have emerged from Czechoslovakia, Romania, Hungary or Turkey since Kurtzke's review. Only four surveys, from Poland, Czechoslovakia, Romania and Estonia in the USSR were graded Class A and these gave estimates of prevalence ranging between 22 and 52 per 100 000 population. The fact that the surveys which employed the best methodology gave the highest estimates of prevalence suggests that the true frequency of the disease in eastern Europe may not be much lower than in the countries of north west Europe.

The results from a recent study in Poland provide a rare counter-example to the general rule that prevalence estimates are higher in second surveys.[56] These investigators reported a fall in prevalence, from 51 to 43 per 100 000 population between 1965 and 1981. The probable reason for the decrease was a marked change in the age structure of the population because of a very high birth rate, rather than any underlying change in the incidence of disease.

In a study of 5 districts in Bulgaria in 1987, the prevalence varied between 10 and 28 per 100 000 population.[57] Both the low rate of disease and the differences between districts may have been the result of under-ascertainment of cases.

No recent data are available for France and Spain. Some of the estimates of prevalence based on earlier work are questionable, either because they depend on small numbers of cases, or because of doubts about the completeness of case ascertainment. For France, estimates of prevalence range between 14 and 63 per 100 000 population. In the single available survey for Spain, in the province of Cataluna, prevalence was estimated at 6 per 100 000 population.

Several studies carried out in Italy before 1975 suggested that multiple sclerosis was uncommon, particularly in the south of the country.[58] This view must now be reconsidered in the light of a series of surveys of small communities on the mainland of Italy[14,59] and in Sicily [10-13] and Sar-

dinia,[60] all of which have reported prevalences of more than 45 per 100 000 population.

Malta, an island less than 100 miles from Sicily, provides an interesting contrast. Here, the prevalence of multiple sclerosis is only 4 per 100 000 population.[61] The population of Malta is about 280 000, which is much larger than that of the towns surveyed in Sicily, but the methods used to identify cases in the two islands were identical and the investigators found that, in Malta, patients with suspected disease of the nervous system were generally fully investigated. It does not seem likely that a difference in prevalence of this magnitude can be explained simply by less complete case ascertainment in the larger Maltese community.

In 1975, Kurtzke suggested that the geographical distribution of multiple sclerosis in Europe could be summarised by considering areas north of the 45° parallel of latitude as a high risk zone and areas to the south as being of distinctly lower risk. Almost all surveys since then have shown a rise in the prevalence of multiple sclerosis, but the size of the increase has been much greater in Italy than elsewhere. A pattern of decreasing risk of multiple sclerosis from north to south is still apparent, especially if allowance is made for the fact that surveys in Italy were carried out in smaller populations than most of the studies in the countries of northern Europe. But no discontinuity in the gradient of risk can be discerned and the notion of a dividing line between zones of risk is no longer tenable.

North America and Canada

The prevalence of multiple sclerosis in Canada and in the northern states of the USA is similar to rates in European countries at the same latitude. A recent study in Ontario, in which multiple sources of information were used to ensure nearly complete case ascertainment, found a prevalence of clinically definite cases of over 80 per 100 000 population.[27] In British Columbia, another study of high quality found a prevalence of 93 per 100 000 population, although this estimate included probable as well as definite cases.[62] In Newfoundland and Labrador, the prevalence of clinically definite and probable cases was 55 per 100 000.[63] A nationwide survey carried out in the USA reported an overall prevalence of 69 per 100 000 population in areas north of the 37° parallel of latitude.[64,65]

Further south, in the North American continent, the prevalence of multiple sclerosis declines. In the nationwide survey, areas south of 37°N were found to have a prevalence of 36 per 100 000 population. These recent data confirm the findings of many earlier studies that demonstrated a decreasing risk of multiple sclerosis from north to south in North America. Several of these surveys were carried out with the express intention of comparing the prevalence at different latitudes using identical methods in two or more places.[30,31,66–69]

Special mention must be made of a series of case-control studies of US ex-servicemen (veterans) from World War II and the Korean conflict.[69] Because these people, whatever their place of origin, had the benefit of similarly high standards of medical care both during and after their period of military service, geographical bias in diagnosis is eliminated. The studies recruited patients from all states in the USA and were able to exploit military records to obtain a control group matched for age, date of entry and branch of service and survival of the war. Table 1.1 shows case-control ratios for the USA for white male ex-servicemen according to place of residence before enlistment. A clear pattern of decrease in risk can be seen from north to south.

The same source of data shows that the risk of multiple sclerosis is considerably lower in the black population of the USA. Overall, the relative risk for blacks as compared with whites was 0.4. The gradient in risk from north to south by place of residence before entry into the Armed Services was also present in blacks.

Table 1.1 The risk of multiple sclerosis in US veterans by tier of latitude of residence at entry to military service. Numbers are case/control ratios

Sex and race	Tier of latitude		
	North	Middle	South
White males	1.41	1.02	0.58
White females	2.77	1.71	0.80
Black males	0.61	0.59	0.31
Total	1.41	1.00	0.53

Central and South America

Apart from a survey of government employees and their dependents in Mexico that showed an extremely low prevalence of the disease (1.5 per 100 000 pop.),[70] no reliable population-based studies of this area have been performed.

Australia and New Zealand

Australia and New Zealand are both countries with evenly high standards of medical care and populations of predominantly European origin. They provide an opportunity to observe whether the gradient of prevalence of multiple sclerosis, which exists in Europe and North America from north to south, is also present in a population of similar racial origins in a different location.

Surveys carried out in Australia in the 1960s suggested that a gradient of risk with increasing latitude did, indeed, exist.[71-73] The direction of the gradient is, of course, reversed in the southern hemisphere, with higher rates being found in more southerly latitudes. Multiple sclerosis was uncommon in Queensland, significantly more frequent in Perth, Western Australia and Newcastle, New South Wales, and commonest of all in Hobart, Tasmania. Any questions about completeness of case ascertainment and the diagnostic criteria that were employed in these studies have been answered by a second series of surveys published recently.[24,74] Following the pattern seen so frequently elsewhere, the prevalence of multiple sclerosis had risen in each of these places, but a gradient of increasing risk from north to south was still clearly present. Current prevalence rates for Australia are given in Table 1.2. Mortality data for multiple sclerosis in Australia have recently been analysed.[75] They confirm the relation between increasing frequency of the disease and increasing southerly latitude. They also show that mortality from multiple sclerosis has fallen in all areas of the country over the past decade. This provides at least a partial explanation for the observed increase in prevalence.

A difference in the risk of multiple sclerosis was also found when areas in the north and south of New Zealand were compared. The prevalence of the disease in Otago and Southland in the most

Table 1.2 Prevalence of multiple sclerosis by latitude in Australia and New Zealand

Location	Latitude	Prevalence (per 100 000 pop.)
Australia		
N Queensland	<23°28'S	12
S Queensland	>23°28'S	21
Perth, WA	32°S	30
Newcastle, NSW	33°S	37
Hobart, Tasmania	43°S	76
New Zealand		
Waikato	38°S	30
Otago and Southland	46°S	79

southerly part of the country was more than twice that in the Waikato Hospital Board area in the North Island[28,76] (see Table 1.2).

South Africa

South Africa is the only other area in the southern hemisphere in which the prevalence of multiple sclerosis has been investigated by population-based surveys. The prevalence is low in all four provinces of the country. There are important differences in the prevalence between different racial groups. Only one case has ever been reported from the black population.[77] Amongst whites, the prevalence is higher (11 per 100 000 pop.) in the English speaking population than in the Afrikaans-speaking population (3 per 100 000 pop.).[78]

Japan

Several, well-performed studies have demonstrated that multiple sclerosis is rare in Japan. Prevalences of less than 5 per 100 000 population have been found in regions situated both in the north and south of the archipelago.[79-81] This low figure is not the result of using different diagnostic criteria or of failure of Japanese neurologists to recognise multiple sclerosis. Neurologists from countries where multiple sclerosis is common (including McAlpine himself) have been involved in some of the surveys. Although higher rates of visual impairment at onset and a higher rate of optic nerve involvement during the course of the disease have been observed in Japanese patients

with multiple sclerosis compared with patients in Western countries, the natural history of the disease is essentially the same.[82] Recently published work gives no indication that the prevalence is increasing.[83]

China and the far East

In Hong Kong prevalence in the Chinese is less than 1 per 100 000.[154] Information from case-series from hospitals providing a neurological service suggests that the disease is also rare in Korea[84] and mainland China.[85]

India

Multiple sclerosis has traditionally been considered extremely uncommon in India. Jain and Maheshwari,[86] who reviewed all work on multiple sclerosis in the sub-continent published before 1985, were able to find only 354 cases collected over a period of 30 years. But a meticulous study of Parsees living in Bombay,[23] where a community of some 14 000 people were screened in a door-to-door survey, suggests that this view may be mistaken. This study found a crude prevalence of 21 per 100 000 population. When age-adjusted to the 1960 population of the USA, the rate was 15 per 100 000. These rates, however, are based on only three cases and their precision is low; the 95% confidence interval surrounding the estimate of prevalence (3.1 to 43.8 per 100 000 pop.) extends from highest to lowest of Kurtzke's zones of risk. There are also indications from case-series that multiple sclerosis may be commoner in Parsees than in other ethnic groups.[87,88] No definite conclusion about the prevalence of multiple sclerosis in India can be reached at present.

The near and middle East

Israel is the only country in this area that has been subject to intensive study with regard to multiple sclerosis. The prevalence in 1960 was 15 per 100 000 population, but the population contains immigrants from more than 70 countries and the rates of disease among them differ considerably according to country of birth.[89,90] The significance of this variation is discussed later.

Estimates of prevalence are available for Arab populations from Kuwait (8 per 100 000 pop.)[91]

and Libya (6 per 100 000 pop.).[92] A case-series from Saudi Arabia indicates that the disease is uncommon there.[93]

Race

The first question to be answered when trying to interpret the global pattern of multiple sclerosis concerns differences in susceptibility to the disease between different races. To what extent can the variation in prevalence of multiple sclerosis throughout the world be attributed to genetically determined ethnic factors?

Whites of European origin

There can be no disagreement about the fact that white people of European stock are susceptible to multiple sclerosis. The highest prevalence of the disease is found in areas of northern Europe and in those countries now populated with people of European descent — North America, Canada, Australia and New Zealand. However, the rarity of multiple sclerosis amongst the white population of South Africa and, to a lesser extent, Queensland and the southern states of the USA, shows that susceptibility alone does not inevitably lead to high rates of disease in white populations.

Blacks of African origin

Multiple sclerosis is almost unknown in the black population of South Africa and what data are available suggest that it is rare over the whole of the African continent. Other black populations manifest higher rates of the disease. The US veterans study provides reliable information about the incidence of the disease in black males in the USA. For all practical purposes, any bias towards underdiagnosis of the disease in blacks is eliminated in this study. The disease is less common in blacks than whites (the relative risk for black males compared with white males = 0.4) but the incidence is far higher than it is in Africa. The declining gradient in risk from north to south observed for whites, also exists for American blacks. This is strong evidence that, even if blacks are relatively protected from the disease by their genetic constitution, the environmental factors causing the disease are similar to those that operate in whites.

Evidence from Jamaica indicates that multiple sclerosis is probably rare in the West Indies[94] and hospital admission rates for multiple sclerosis in first generation West Indian immigrants in Britain are very low.[95,96] This must be set against the findings of a recent study of second generation black immigrants in London (i.e. blacks of West Indian origin born in the UK) which suggests that the incidence of multiple sclerosis is as high in this group as it is in the native white population.[97]

A possible reason for the higher rates of multiple sclerosis observed in blacks of the USA when compared with rates in Africa is that, as a result of interbreeding with the white population, they have become more susceptible to the disease. But this explanation cannot account for the very rapid increase in the frequency of multiple sclerosis, within one generation, that has occurred in West Indians in London. The evidence that black people have an innately low susceptibility to multiple sclerosis is far from conclusive; the low rates of the disease observed in some black populations may be explicable in terms of different exposure to environmental factors.

Orientals

Rates of multiple sclerosis are very low in Japan and evidence from Hong Kong, China and Korea suggests that the disease is rare in other oriental populations. Death rates from multiple sclerosis in Japanese and Chinese immigrants in California and Washington are about 4 times lower than for the white population. The numbers of deaths on which these rates are based are very small,[98] but subsequent prevalence surveys of the same areas identified only 8 cases of multiple sclerosis out of a total population of 120 066 Japanese-Americans.[99] An intensive search was made amongst the Japanese communities living in these areas and it is not likely that the low prevalence of the disease is due to under-ascertainment of cases. Nor can the deficiency of cases be explained by a shorter duration of disease in the Japanese than in the whites. The Japanese living in these American cities do not tend to cluster into tight ethnic communities and, with the possible exception of diet, the investigators could not identify any environmental factors that might operate

among the Japanese but not amongst the white population. A low prevalence of multiple sclerosis has also been found in Japanese, Chinese and Filipino immigrants in Hawaii.[100]

The data are highly suggestive that the Japanese and probably other oriental groups too, possess low susceptibility for multiple sclerosis and that this has a genetic basis. However, the effect of migration on risk of disease is sometimes delayed. The incidence of gastric cancer, for example, is lower in the second generation of Japanese immigrants to the USA than in the first, but still higher than in American whites.[101] Final confirmation of low inherent susceptibility must await studies of occurrence of multiple sclerosis in third generation American Japanese who have fully adopted the way of life of their host country.

Arabic peoples

Unfortunately, there are no data which allow the possible contribution of protective genetic factors to the low rates of multiple sclerosis in arabic countries to be assessed.

People from the Indian sub-continent

Evidence from hospital discharge rates in the United Kingdom suggests that immigrants from India and Pakistan retain the (probably) low risk of multiple sclerosis of their countries of origin.[95,96] The population in this study however, consisted mainly of first-generation immigrants and their period of residence in the United Kingdom may have been too short for any change in risk of the disease to become apparent. For this group the question of racial susceptibility, or lack of it, remains open.

Maoris

A recent survey in New Zealand failed to identify any cases of multiple sclerosis in the Maori population.[28] Ethnic differences in access to specialist medical services were not considered great enough to explain this finding. The current way of life of Maoris was said by the investigators to be similar to that of the European population and, if this is correct, it may indicate a genetic

developed no doubt in response to some need which may be detected in the course of enquiry but which can seldom be fulfilled. Caplan & Nadelson[133] present two very instructive case histories of patients with undoubted mild multiple sclerosis who became incapacitated by non-organic symptoms. They mention a common feature of such cases, very active involvement in the affairs of the Multiple Sclerosis Society. There is nothing to be gained and perhaps much to be lost in disturbing this way of life.

APHASIA

Aphasia is uncommon in multiple sclerosis and, indeed, Kurtzke[25] wrote that he had never seen a well-documented example. He regarded the presence of aphasia as evidence against the diagnosis. The frequency of aphasia in representative reported series has been 1% by Poser,[53] 1% by Kahana et al[133] and one of 145 cases.[135]

The advent of CT scanning has led to the increasing recognition of multiple sclerosis presenting in a manner clinically and radiologically indistinguishable from a malignant brain tumour p. 63) and in such cases aphasia is commonly present if the dominant hemisphere is involved. As early as 1902, Gussenbauer[136, 137] reported such a case, where the history and findings, that included aphasia, strongly indicated a left hemisphere tumour, but at post mortem only multiple sclerosis plaques were found. Remitting aphasia has been described in a number of such cases.[138-140] Aphasia may be accompanied by alexia and agraphia.[141] Apraxia for speech — aphemia — without aphasia has been described as the presenting symptom of multiple sclerosis,[142] but the clinical diagnosis has been disputed.[143]

EPILEPSY

Fits or seizures appear in virtually every list of symptoms of multiple sclerosis either at the onset or in the course of the disease. The proportion of patients affected is never large but epilepsy is perhaps a surprising effect of a disease process predominantly affecting white matter. Tables of symptoms are naturally not accompanied by clinical descriptions either of the evidence of multiple

sclerosis or the nature of the seizures. There are a number of possible sources of error.

Epilepsy is common in young adults, certainly much more common than multiple sclerosis, and coincidental association must occur. Two such cases were described by Matthews.[144] In one patient, epilepsy had begun at the age of 12 and symptoms of multiple sclerosis at 41, while in the other patient epilepsy at 14 had been followed by multiple sclerosis at the age of 20. The possibility that the chronic recurrent major fits had been the initial symptom of multiple sclerosis must be discarded, as in both patients the EEG contained symmetrical 3 per second spike and wave discharges.

In another patient in this series in whom psychomotor fits developed in the course of clinically definite multiple sclerosis a temporal lobe astrocytoma found at autopsy was thought to be the cause, although numerous multiple sclerosis plaques were also present.

In the past there has certainly been confusion with unilateral tonic seizures[145] now thought unlikely to be epileptic as this word is normally understood. In earlier reports these paroxysmal symptoms have sometimes been regarded as Jacksonian motor fits.

Nevertheless there remains a small proportion of patients in whom the diagnosis both of epilepsy and of multiple sclerosis can be established and a causal connection accepted.

Early reports were reviewed by Matthews.[144] Writing in 1962, 65 case reports were found in which both the grounds for the diagnosis of multiple sclerosis and some description of the fits were given. It was evident that the sources of error described above had not been entirely avoided. The paucity of post mortem confirmation so often found in clinical studies of multiple sclerosis was particularly pronounced, only seven reports being found. In one, the diagnosis did not appear to be multiple sclerosis and one patient could not be said with certainty to have had epilepsy. Two patients certainly had both conditions but the relation between the two was obscure: for example, one patient had sustained a serious closed head injury some years before the onset of the fits. In the remaining three cases a causal connection could be accepted but both the clinical features and

much less unpleasant than trigeminal neuralgia and remit completely after a few weeks or months. They may be referred to by the patient simply as 'dizziness' only revealed more exactly on close questioning. The paroxysms may occur as the initial symptom of multiple sclerosis,[188] in the absence of physical signs[191] or more usually during the relapsing and remitting stage of the disease. They are so characteristic that the diagnosis of multiple sclerosis must be strongly suspected even if further evidence of the disease is not apparent. Indeed Wolf & Assmus[189] regarded them as pathognomonic. The differential diagnosis is with transient ischaemic attacks involving the brainstem, but the extreme brevity and frequency of the paroxysms are distinctive. The response to treatment is described below.

Tonic seizures

Tonic seizures were first recognised as a characteristic feature of multiple sclerosis in 1958.[145]. Earlier descriptions can be found but the remarkable attacks were not recognised for what they were. Determan[192] described identifiable tonic seizures in a patient he believed to be suffering from the neurological effects of influenza, but the partial Brown-Séquard syndrome was more probably the result of multiple sclerosis. Redlich[193] described two cases of what he regarded as hemitetany in multiple sclerosis and Störring[194] included two cases of unilateral tonic seizures in his series of epilepsy due to multiple sclerosis. He referred to these as Jacksonian epilepsy but specifically mentioned the 'Pfötchenstellung', the tetanic posture of the hand. Guillain et al[195] also described painful unilateral tonic spasm in a patient with a form of neuromyelitis optica. At autopsy three necrotic lesions were found, and a diagnosis of multiple sclerosis cannot be regarded as certain. Possible examples were briefly described by Williams et al[196] and by Fugelsang-Frederiksen & Thygesen.[197]

The original description was confirmed in a further four cases by Joynt & Green[198] and it has since become apparent that these strange attacks are relatively common. The original description was of 4 cases seen within two years, 2 of them being patients of the same general practitioner. As

these were the only cases of multiple sclerosis under his care, he came to regard tonic seizures as a usual feature of the disease. Exactly how commonly they occur is not easy to establish as they are probably sometimes described by patients and their medical attendants as cramps. In British cases, tonic seizures had occurred in 4% of 204 cases at the time of reporting.[190] Espir et al[190] found 8 cases in 600 patients with definite or suspected multiple sclerosis. In a personal series of 377 patients, tonic seizures had occured in 14 (3.7%), a frequency identical to that of paroxysmal dysarthria and ataxia. In Japan, however, tonic seizures are much more common, occurring in 17%[66] or even 28% of cases.[226]

Tonic seizures usually conform to the general pattern of paroxysmal symptoms in appearing suddenly, occurring frequently and eventually remitting completely. Different patterns have been described, with seizures occurring in repeated clusters[199] or infrequently over several years.[186] The individual seizures are often triggered, apparently by movement, but it is naturally difficult to determine whether it is the motor activity or the consequent sensory stimulation, such as that resulting from putting the foot to the floor, a common trigger, that is effective.

Attacks may also occur spontaneously and can be induced by overbreathing.

Seizures are usually stereotyped for individual patients, although there may be degrees of severity and extent of the spasm. The spasm may be preceded by sensory symptoms, characteristically affecting the limbs or trunk on the side opposite the muscular spasm. These may be described as burning or tingling but are always unpleasant. The tonic contraction may affect one or both limbs on one side and often the face. Nearly always, spasm begins in one limb but spread is rapid. The posture adopted is often that of tetany but there are variations: the fingers may be flexed at distal joints rather than extended, the upper limb is flexed at the elbow and usually abducted at the shoulder. The lower limb is extended at all joints. The face is contracted, probably involuntarily, but it may also be contorted by pain. Pain in the affected limbs may indeed be extremely severe but is not invariable, some patients merely complaining of discomfort.

In all cases personally observed tonic seizures have been unilateral and this appears to be the case in Europe and North America. However, in Japan tonic seizures are not only more frequent but are often more severe, being bilateral and intensely painful.[66] In the only reported case from Africa, the spasm was also bilateral. Tonic seizures may occur concurrently with other paroxysmal symptoms, particularly with dysarthria and ataxia.[186]

The duration of tonic seizures may be as long as two minutes and the frequency does not attain that sometimes seen in paroxysmal dysarthria. Their pathophysiology is discussed on p. 235. It is unlikely that tonic seizures of this kind occur only in multiple sclerosis, but journals now seldom allow space for descriptions of purely clinical phenomena. Earlier reports of forms of 'subcortical epilepsy' were reviewed by Matthews.[145] Durston & Milnes[201] described similar attacks in patients thought to have relapsing encephalomyelitis but the dividing line from multiple sclerosis is imprecise. In context, tonic seizures are unmistakable evidence of multiple sclerosis and on one occasion led to my telling a patient that this was the diagnosis, in the complete absence of physical signs.

A woman of 26 had experienced two episodes of optic neuritis six and five years earlier, with complete recovery of vision and normal optic discs. One year before being seen she had Lhermitte's sign for some three months. She was referred because of right sided tonic seizures affecting mainly the upper limb but frequently triggered by putting the right foot to the ground. The attacks were unpleasant but not painful. There were no abnormal physical signs. However, after 20 deep breaths a typical tonic seizure was induced exactly as in her spontaneous attacks. The history was thought to be pathognomonic and at her urgent request the diagnosis was discussed.

Paraesthesiae

Sensory symptoms ranging from tingling to severe pain may accompany tonic seizures and the former commonly form part of the brainstem syndrome of paroxysmal dysarthria. It is not therefore surprising that paroxysmal paraesthesiae or dysaesthesia can occur in isolation but being entirely subjective, these are much more difficult to recognise. In a

personal example[186] the initial symptom of clinically definite multiple sclerosis was an extremely severe quivering sensation beginning on the right side of the face and spreading to the right arm, index finger and thumb. These attacks lasted a few seconds but built up to such extreme frequency that his doctor had to be summoned twice in one night. The sensations, which he insisted were not painful, responded immediately to treatment with carbamazepine. Evidence of multiple sclerosis was not long delayed but to anyone unfamiliar with the paroxysmal symptoms of the disease, diagnosis was scarcely possible at the onset. Osterman & Westerberg[185] mentioned a patient with episodes of numbness as the initial symptom of multiple sclerosis but did not elaborate on how this sometimes misleading word should be interpreted. Espir & Millac[190] described a paroxysmal burning sensation in one lower limb and mentioned two less convincing cases of isolated sensory paroxysms. It is probable that the paroxysmal nature of sensory symptoms is only detected when obtrusive. Segmental paroxysmal dysaesthesiae appear to be relatively common in Japan, as Yabuki & Hayabara[202] were able to report 7 examples.

Pain

Paroxysmal pain has been reported rather more frequently[190,185,203] as an isolated or virtually isolated symptom. The pain characteristically involves a stereotyped segment of one limb, more usually the arm, but has been described in the perineum.[204] It is sometimes less easy to characterise as paroxysmal in that the duration of attacks may be longer and the response to carbamazepine is less assured. There is also room for diagnostic confusion with other forms of episodic limb pain unrelated to multiple sclerosis but sometimes responding to appropriate treatment.

Here is an example of paroxysmal pain following a different form of paroxysm at the onset of multiple sclerosis.

A woman of 28 presented with a 3-month history of attacks occurring about six times a day in which she experienced a strange sensation in the left upper lip and side of the nose accompanied by inability to use the right hand for about 30 seconds. If she was walking, the right leg would drag for a few steps.

Speech was not affected. Examination showed only minimal clumsiness of the right hand but multiple sclerosis was suspected and carbamazepine prescribed. These attacks stopped almost immediately but she then began to experience daily attacks of pain, beginning in the left side of the neck and spreading to the left upper arm. The pain would build up slowly, eventually becoming very severe and lasting for about one hour. There were no additional abnormal signs. Some improvement followed increased doses of carbamazepine but severe attacks continued about once a week for 6 months. Three years later she developed internuclear ophthalmoplegia and an ataxic gait. Oligoclonal IgG was present in the CSF.

Itching

Paroxysmal itching in multiple sclerosis was first described by Osterman & Westerberg[185] in 1976 although itching was mentioned as an initial sensory symptom by McAlpine.[10] Subsequent reports[202,205,206] have confirmed the paroxysmal nature of the symptom although, as with pain, the natural history may differ in some respects from the accepted pattern in that in some patients the attacks are more prolonged, 20 minutes or longer, and the response to carbamazepine is sometimes disappointing. Itching has been described in the upper and lower limbs and on the face and trunk.

In a personal series of 377 patients, 17 experienced paroxysmal itching, in one as an isolated initial symptom. Itching affected the upper limbs alone in 8, usually one shoulder region or a localised area of the forearm. In 5, the lower limbs were affected, most commonly one or both thighs. One patient had itching of one side of the scalp. In the remaining 3 patients, more than one area was involved: right face and shoulder, left forearm and abdominal wall and right side of the neck, and bilaterally on the trunk and arms. In 9 patients, changes in cutaneous sensation were present in the affected area.

Paroxysms may be spontaneous or induced by sensory stimulation or movement. The itching is intense, leading to vigorous but ineffective scratching to the extent of excoriating the skin. One patient used a wire brush in an attempt to control the itch. Between the paroxysms there may be persistent dysaesthesia or even some blunting of cutaneous sensation in the same area. In one

case reported by Yamamoto et al[206] either or both shoulders would be affected, unlike the usual constant form of paroxysmal symptoms.

Itching may be associated, either simultaneously or in sequence, with other paroxysmal symptoms including tonic seizures or trigeminal neuralgia.[206]

Diplopia

Diplopia may occur with other symptoms of brainstem disturbance in paroxysmal dysarthria. It has also been described as occurring as an isolated symptom.[185] Both as an initial symptom or during the course of the disease, diplopia is peculiarly difficult to recognise as paroxysmal. Momentary double vision is a common complaint in those who believe, incorrectly, that they are developing multiple sclerosis and may also occur with fatigue in patients with latent squint. In established multiple sclerosis, fatigue and changes in environmental temperature will also cause transient recurring diplopia. In convincing cases double vision has occurred many times a day and has lasted for up to a minute. Dysjunctive movement was illustrated by Matthews[186] as forming part of a complex paroxysm of brainstem signs. Paroxysmal ocular flutter may cause blurred vision.[207]

Akinesia

Paroxysmal loss of use of one or more limbs is also encountered. There is naturally some difficulty in distinguishing such symptoms from those of ataxia or even from some of the less severe forms of tonic seizure. This remarkable symptom is usually, however, instantly recognisable even in the total absence of evidence of multiple sclerosis. This is exemplified by the man of 25 who complained of frequent sudden episodes of complete inability to take a further step. This usually occurred almost immediately he had risen to his feet. In observed attacks he would stand quite still for a few seconds before stepping out again. The attacks were immediately abolished by carbamazepine. There was no other evidence suggestive of multiple sclerosis. Zeldowicz[208] described 12 patients with 'paroxysmal motor episodes' in all as the first symptom of multiple sclerosis, in fact with a mean interval of nine years before the appearance of further signs

stereotactic surgery but this was followed by inability to swallow. The diagnosis was confirmed at autopsy, the myoclonus being attributed to lesions involving the red nucleus. Mouren et al[229] and Herrmann & Brown[230] have described palatal myoclonus in multiple sclerosis and there is a brief reference to episodic segmental myoclonus.[231]

Spasmodic torticollis associated with multiple sclerosis was described by Guillain & Bize[232] and has occasionally been reported since,[233,234] although a causal connection has not been established. Focal dystonia and writer's cramp have also been described.[234]

HEADACHE

Headache appears in most lists of symptoms of multiple sclerosis but with remarkable variations in frequency and usually without any attempt to define the type of headache or how it is thought to be related to multiple sclerosis. Abb & Schaltenbrand[20] reported headache in 32.5% of patients but their information was obtained largely by correspondence. In the comparative study of autopsy proven cases of multiple sclerosis from different countries,[16] headache did not appear at all as a symptom in British cases, in 19% of those from Norway and 12% of patients in the USA. Poser[53] does not include headache in the list of symptoms analysed. Kurtzke[25] found headache common in the onset bout, but remarked that it was usually associated with visual or brainstem signs.

Clifford & Trotter[54] reported that 17 of 317 patients with multiple sclerosis suffered from severe headache but this was not thought to be due to the disease. Migraine has been thought to be unduly common in multiple sclerosis[235] and Freedman & Gray[236] found that in 44 of 1113 cases, onset or relapse had been heralded by headache that they regarded as of vascular type. Seventeen of these patients had a previous history of migraine. Headache was most commonly associated with signs of a progressive posterior fossa lesion, sometimes causing diagnostic difficulty.

Bonduelle & Albaranès[135] defined the type of headache that they attribute to multiple sclerosis, in 5.5% of their cases. They excluded vague discomfort around the orbit in optic neuritis but it is not clear whether they included the by no means vague frontal pain sometimes experienced in this condition. They accepted headache of recent onset preceding or accompanying definite signs of relapse. In three patients headache was the initial symptom.

In the absence of definitions nothing can be learnt from the comparison of different series, as differences will depend on methods of enquiry and interpretation and perhaps on relative national fortitude.

Headache is certainly a feature of acute 'pseudotumorous' multiple sclerosis[237] and in such cases does not differ from that of other causes of raised intracranial pressure. Kahana et al[134] do not mention headache as a symptom of 'cerebral' multiple sclerosis.

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system may preserve function, but this explanation can scarcely be invoked in the optic nerve. It is more probable that sufficient conduction can be maintained or restored in demyelinated axons, as described above. Remyelination obviously cannot be claimed as the mechanism of preserving function in areas demonstrated histologically to be demyelinated.

MRI

The pathological basis of the abnormalities seen on MRI has attracted much discussion. It was established early that abnormalities shown by scanning the brain post mortem matched the chronic demyelinated gliotic plaques found on sectioning the brain.[96] It is obviously much more difficult to establish the pathology of the acute and often transient abnormalities seen in active disease. Although these appearances are more frequent in relapse, they are seldom related to the clinical features and frequently develop in the complete absence of any other evidence of activity.[97] Lesions may appear in previously unaffected areas or existing lesions may expand. Occasionally, several fresh lesions appear together but it is common for some to increase in size while others are fading.

T_1 and T_2 relaxation times depend on the concentration and behaviour of protons almost exclusively those in the hydrogen of water. The responses can be modified by the chemical environment but, in general, the abnormalities seen on the scan indicate an excess of water, a highly non-specific finding. An increase in water content could result from an influx of cells or, much more probably, from oedema. Whether demyelination could produce an identical signal is unknown but considered unlikely.[94] Despite the similarity of the MRI signals, the histopathology of acute evanescent lesions would naturally be expected to differ from that of chronic gliotic plaques. The interesting possibility that the former are not, at least initially, plaques of demyelination but areas of inflammation and oedema has been raised.[98,99] Repeated episodes of asymptomatic breakdown of the blood-brain barrier are envisaged as eventually leading to demyelination and symptomatic relapse. Miller et al[100] also discuss the changes responsible for the MRI signals from acute and chronic

lesions. Excess water increases both T_1 and T_2 but the presence of protein shortens T_2 but not T_1. Vasogenic protein-rich oedema fluid might be expected in acute enhancing lesions and would result in a relatively high T_1/T_2 ratio. Their findings show very low ratios in some non-enhancing lesions, but the degree of overlap provides little support for their hope that relaxation time measurements would distinguish recent from chronic lesions or, indeed, throw much light on the nature of the pathology. The presence of excess water in chronic, non-enhancing lesions is not well understood. Even if the existence of a form of normal pressure hydrocephalus in multiple sclerosis[101,102] is accepted, this could not explain excess water in chronic lesions remote from the ventricles. A persistent defect in the blood-brain barrier is a possible explanation, but this is not indicated by gadolinium enhancement. In the original demonstration of breakdown of the barrier in multiple sclerosis by Broman,[103] trypan blue dye entered all types of plaque, both recent and chronic. Absence of enhancement in chronic lesions cannot with certainty be interpreted as indicating an intact blood-brain barrier. Quantitative MRI scanning[104] has shown excess water in normal-appearing white matter in multiple sclerosis, which was reduced by steroid treatment, although the signals from chronic lesions were not altered. Oedema is a common feature of the acute plaque[105] and may be of such severity as to cause ventricular displacement[106] or swelling of the spinal cord.[107] Compression of nerve fibres leading to reversible conduction block is a highly probable consequence. The rapid effect of corticosteroids both in abolishing enhancement of lesions shown by CT[108] and in resolving symptoms of relapse has been attributed to repair of the blood-brain barrier and resulting relief of oedema. Corticosteroids are extremely effective in the relief of oedema around a cerebral tumour and consequent reversal of gross physical signs and a similar acute effect is probable in multiple sclerosis. Steroid treatment does not, however, appear to influence gadolinium enhancement of MRI[109] and, on this evidence, relief of oedema is not accompanied by restoration of the blood-brain barrier. To what extent natural remission extending over many weeks can be attributed to the clearing of oedema is unknown. In

stimulation but the effect did not at first appear to be related to the activity of multiple sclerosis in the patients. Later they found that inhibition was more marked using serum from patients with active disease. The activity was thermolabile and was present in the serum IgG fraction, these properties suggesting that it was an antibody. The effect was not produced by normal serum or by serum from patients who had recently suffered a stroke as had been reported.[124] The site of action was shown to be on synaptic transmission and no effect was observed on conduction in myelinated or demyelinated fibres.

Serum neuroelectric blocking activity is not, however specific for multiple sclerosis, being present to a similar degree in motor neurone disease.[125] In both diseases, activity was higher than in controls but there was much overlap of individual values. The sudden onset of symptoms is by no means characteristic of motor neurone disease and these findings must throw considerable doubt on the relevance of neuroelectric blocking agents to the pathophysiology of multiple sclerosis.

REMYELINATION

It was long held as dogma that remyelination did not occur in the central nervous system[126] and therefore could not account for remission in multiple sclerosis. However in experimental animals remyelination occurs, often rapidly, after a great variety of physical, chemical and immunological insults to the central nervous system,[127] including chronic relapsing EAE, the supposed model of multiple sclerosis. These observations were made by examining batches of animals killed at increasing intervals from the event causing demyelination. An approximation of this method was achieved by Prineas et al[128,129] who examined lesions in patients with the acute form of the disease dying at intervals from clinical onset ranging from less than 3 months to 5 years. Within 3 months of onset there were many areas of obvious myelin breakdown, with depletion of oligodendrocytes. Such areas of active demyelination were less frequent in patients who had survived rather longer. Plaques in which all fibres were thinly myelinated to the same degree, with

short internodes, were increasingly common in patients dying 3–18 months from onset and were interpreted as showing remyelination. Shadow plaques, in which myelin sheaths stain poorly and are unduly thin, have usually been regarded as resulting from partial demyelination,[130] but both Lassmann[131,132] and Prineas[128] believe that they are remyelinating, although subject to reinvasion by disease.

Prineas' claim[128] that his observations are in temporal sequence in a manner comparable to animal experiments cannot be fully justified as it is increasingly apparent that onset of disease usually, or perhaps always, antedates onset of symptoms by an unknown period. Nevertheless, the findings provide support for the commonsense view that remission is the result of remyelination.

In chronic multiple sclerosis the picture is different, although shadow plaques may still be seen. A few fibres with thin myelin sheaths can be seen at the periphery of some chronic plaques[133] and it is probable that some remyelination occurs. Some degree of remyelination by Schwann cells also takes place, particularly in the spinal cord.[134] This strange phenomenon has been investigated experimentally[135,136] but it has not been shown that conduction can be restored in this way. The large areas of rapid remyelination by oligodendrocytes observed by Prineas et al,[129] if their interpretation is correct, are no longer present and, of course, clinical remission has usually long ceased. Progressive disease may therefore be attributed to failure of the remyelination that occurs in the relapsing and remitting stage. If this is so, the reason for this failure is obviously of great interest. It has been attributed to a variety of defects of function or proliferation of oligodendrocytes, but no conclusion has been reached. Gliotic scarring probably does not inhibit myelination, as Lassmann[131] found gliotic areas resembling plaques but fully myelinated and presumably remyelinated.

Axonal changes

It is characteristic of the early multiple sclerosis lesion that there is little or no axonal degeneration. The extent of axonal loss in long-established plaques has been a matter for controversy, to some

extent because of difficulties with staining techniques. It is commonly presumed that permanent loss of function is due to axonal degeneration and is therefore irreversible. The evidence for this assumption is not compelling and even exhaustive accounts of the pathology of multiple sclerosis make little reference to the fate of the axons.[130] Using a staining technique for neurofibrils, Greenfield & King[137] found that only 10% of plaques showed severe reduction in numbers of nerve fibres. Peters[138] remarked on the relatively infrequent secondary ascending or descending degeneration of axons in tracts within the spinal cord, even in the presence of extensive demyelination, and that he had never found such axonal degeneration to be complete.

Using fundus photography, however, MacFadyen et al[139] have demonstrated extensive axonal loss in the retinal nerve fibre layer in a high proportion of patients with multiple sclerosis, indicating that the pathological changes in the optic nerve are not confined to demyelination. This finding may demand some reinterpretation of the pathophysiology of persistent visual defects after optic neuritis.

The glia

The glial reaction in multiple sclerosis, an obviously important component of the disease process, is described in Chapter 12. It is not known or at present conjectured that astrocytic proliferation has any direct role in the causation of symptoms.

Conclusion

The reinstatement of remyelination as a probable immediate cause of the remission of symptoms has done much to clarify ideas on the pathophysiology of multiple sclerosis. Much, however, remains to be explained and the evidence from MRI of ceaseless asymptomatic activity is disquieting.

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lived activation products C3a and C4a can be detected in the spinal fluid of patients with multiple sclerosis, but not in controls.[134] There is a significant reduction in the concentration of C9, implying complement activation, and consumption[135,136] which correlates inversely with increased IgG synthesis. The concentration of C9 increases at the time of improved clinical status resulting from treatment with high dose intravenous methylprednisolone.

Evidence that complement activation occurring in patients with multiple sclerosis involves the formation of membrane attack complexes is provided by the detection of the membrane attack complex neo-antigen, which only forms when the terminal complex is fully assembled through the sequential addition of C5b C9.[137] Following demonstration of the recovery mechanism of oligodendrocytes and the identification of vesicles in the supernatant of cells grown in tissue culture, identical particulate material has been found in the cerebrospinal fluid of patients with multiple sclerosis, but not in individuals with mechanical nerve root irritation or intracranial mass lesions.[130] These vesicles bind C8, C9 and the neo-antigen of membrane attack complexes, but not C3 and are shown by electron microscopy to have a high concentration of membrane pores; galactocerebroside but not myelin basic protein is present on their surface.

THE ROLE OF MICROGLIA AND MACROPHAGES IN MULTIPLE SCLEROSIS

Histological evidence suggests that macrophages are ultimately responsible for contacting and stripping away myelin from axons.[138,139] Vesicular disruption of myelin occurs in proximity to macrophages and the myelin lamellae are removed by a process which involves the attachment of myelin to coated pits, after which the sheets are incorporated into macrophages as elongated vesicles. The presence of coated pits suggests that this process is receptor-mediated and macrophages seen to contact oligodendrocytes and the myelin sheath are coated with antibody. The source of these macrophages is controversial. The intact central nervous system is traditionally regarded as not containing cells which are primarily immunocompetent, but during development, circulating macrophages enter the nervous system, seemingly through an intact blood–brain barrier in response to neuronal death, and establish themselves as resident microglial cells.[140] Thereafter, it can be difficult to distinguish one cell type from the other and no substantial differences may exist. Circulating activated macrophages can also cross the blood–brain barrier and so contribute to the local inflammatory process.

Therefore, the implication is that the mature central nervous system contains large numbers of cells which are capable of secreting and responding to a wide range of inflammatory mediators: in addition, they have the ability to phagocytose intact cells and debris.[134] The list of soluble factors which interact with macrophages is enormous. Interferon gamma, produced in response to viral infection, is a potent activator of macrophages and stimulates the release of interleukins, tumour necrosis factors, toxic oxygen species and some early complement components;[134] it also activates macrophage-mediated cytotoxicity. Many of these cytokines and inflammatory mediators form part of powerful positive feed forward loops; thus complement activation leads to the production of activation products which are chemotactic for and activate macrophages, which in turn produce more early complement components. Conversely, the production by macrophages of other molecules such as prostaglandins, which are immunosuppressive, is reduced by interferon gamma. Several of these macrophage products, including tumour necrosis factor, leukotrienes and oxygen radicals have been shown to damage myelin in vitro either by a direct effect or through oligodendrocyte injury.[141,142]

Complement activation, intrathecal antibody synthesis and other pro-inflammatory cytokines provide the local conditions needed for macrophage activation. What remains uncertain is whether macrophages activated damage to myelin and oligodendrocytes or merely act as scavengers of tissue that is already irreversibly injured through humoral mechanisms of immunity.

CONCLUDING REMARKS

The hypothesis that emerges from a consideration

of the evidence available from human samples and experimental studies is that in genetically susceptible individuals, activated T cells and macrophages, responding to environmental triggers, increase their normal surveillance of the nervous system and interact with type 1 astrocytes further to disrupt the blood–brain barrier and cause a leak of immune mediators into the nervous system. Oligodendrocytes are unduly sensitive to contact with complement, especially when antibody directed against a variety of surface components of the oligodendrocyte or its myelin processes is also present. The interaction of these soluble mediators increases membrane permeability and leads to a rise in intracellular calcium, the degree and duration of which determines whether or not reversible injury ensues. As complement activation proceeds, macrophages are recruited and they contribute to cell injury through release of cytokines and phagocytosis of the myelin lamellae. The sequence of events that leads to tissue injury needs to be understood so that a mechanistic approach is taken in selecting new treatments and the resource of patients available for the clinical trials, on which definitive strategies for treatment will be based, is not squandered.

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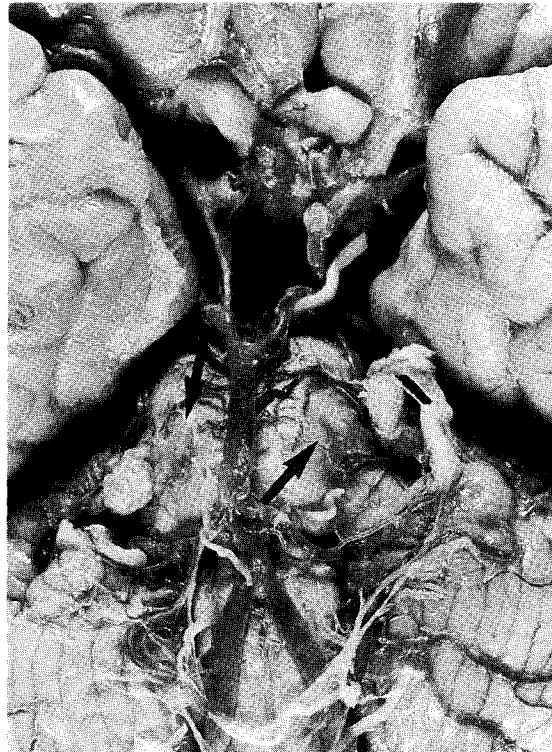**Table 12.1** Significant complications in multiple sclerosis

Complication	Number of cases
Bronchopneumonia	55
Cystitis and pyelonephritis	53
Renal and/or vesical calculi	10
Pelvic abscess and localised peritonitis	9
Venous thrombosis: leg veins	5
periprostatic	3
adrenal vein	1
renal vein	1
cerebral vein	1
Pulmonary emboli	6
Adrenal haemorrhage	1
Stercoral ulceration	1
Volvulus	2
Bacterial endocarditis	1
Hypothermia	1
Epilepsy	1
Burns	1
Suicide	3

Fig. 12.2 Plaques seen externally on the surface of the pons (arrows) after stripping of the leptomeninges.

patients die with extensive pressure sores or septicaemia complicating renal sepsis, and not all patients die as a direct result of their disease; in a series of 120 cases, collected over many years, approximately 25% of patients died from apparently unrelated conditions.[10]

The essential lesion — anatomy and evolution

Anatomy of plaque distribution

In classical multiple sclerosis, in which the patient has been severely affected and has had many years of illness, the brain at autopsy may appear slightly atrophic with widening of cerebral sulci and some ventricular dilation, and the spinal cord may also show some atrophy. The characteristic specific pathological abnormality is the presence of scattered demarcated lesions in which periaxial demyelination can be demonstrated histologically. Irregular, grey, firm depressed plaques can often be seen externally in the optic nerves, on the surface of the pons, (Fig. 12.2), medulla and spinal cord, and on the superior surface of the corpus callosum. These may be up to 5 mm in diameter

and are best seen if the arachnoid is stripped from the underlying surface.

In the unfixed, sectioned brain, old lesions are grey, often somewhat translucent and firm (hence the use of the term 'sclerosis'), and recent lesions are soft and appear pink: after fixation, the distinguishing hardness of the old lesion is lost and the recent lesions are difficult to see.

The pattern of plaque distribution varies considerably from case to case and within any one case plaques may vary considerably in size and age. A clear impression of the most common distribution of lesions within the brain is best obtained by the study of a series of cases, altering in each the plane of cerebral section. Thus, with coronal sectioning, a wide scatter of lesions is seen in both cerebral hemispheres, often with a degree of symmetry (Fig. 12.3); predominant involvement of one hemisphere is rare. The relationship of plaques to the ventricular system is striking, particularly to the lateral angles of the lateral ventricles and to

a

b

c

d

e

Fig. 12.1 a Schematic drawing showing relationship of the oligodendrocyte, myelin sheath and axons. *lost in periaxial demyelination; ' preserved in periaxial demyelination. b Multiple sclerosis; established lesion showing myelin loss. Spielmeyer fat × 70. (Reproduced with permission from Allen 1984[23]). c Multiple sclerosis; established lesion showing axis cylinder preservation. Bielschowsky × 80 (Reproduced with permission from Allen 1984[23]). d Periaxial demyelination in multiple sclerosis; a thinly myelinated nerve fibre (arrow) shows irregular blebbing and displacement of myelin as it traverses an astrocytic scar. Electron micrograph × 6250. e Loss of a myelin internodal segment in multiple sclerosis can leave paranodal axolemmal specialisations in place (between arrows). Filament-rich astrocytic processes surround the axon. Electron micrograph × 6800. (Reproduced with permission from Allen 1984[23].)

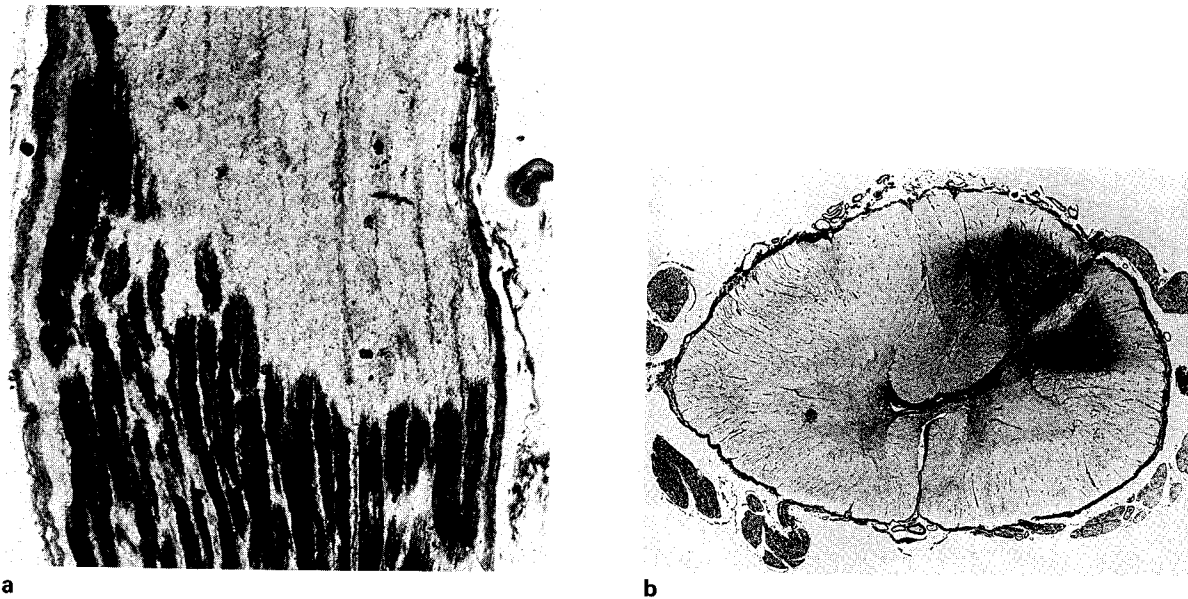**Fig. 12.36** Dévic type multiple sclerosis. **a** Demyelination of optic nerve. Spielmeyer × 65. (Reproduced with permission from Allen 1984[23].) **b** Severe demyelination of the cervical cord. Spielmeyer × 10.

Hughes (1978)[107] has collected a series of cases of acute necrotic myelopathy and has reviewed a further 20 well-documented cases. These may well be examples of demyelinating disease and this view is supported by a previous history of optic neuritis in one case and of associated plaque formation in the brain of a second case.

SUMMARY AND SIGNIFICANCE OF THE PATHOLOGICAL LESIONS IN MULTIPLE SCLEROSIS

Anatomical and histological findings

To the non-histologist, detailed descriptions of the plaque in multiple sclerosis and of mechanisms of demyelination must be confusing. While acknowledging the dangers of oversimplification, an attempt has been made to summarise salient features (Fig. 12.37, Table 12.2) and to indicate possible primary or secondary significance.

A constant and well-documented feature of multiple sclerosis is the anatomical distribution of the lesions, and many studies have confirmed the susceptibility of myelin in the periventricular region and in the optic nerves and spinal cord, yet the significance of plaque distribution is unknown. The susceptibility of the periventricular white matter has been explained on the basis of a circulating toxin or an antibody effect. Not all periventricular white matter is equally vulnerable, however, and a recent study[108] suggests that the periventricular plaque results from the formation of a lesion around a subependymal vein, which later coalesces with adjacent lesions. These workers argue that, as there is no origin of plaques from ependyma, it is unlikely that CSF plays a part in their initial development. Chronic lesions often show an overlying granular ependymitis and this inflamed ependyma could secondarily allow molecular exchange between plaque and CSF.

The relationship of plaques to veins and venules is a continuing theme in the literature and is supported by the careful anatomical studies of Fog,[109] who observed that most plaques had a close anatomical relationship with one, two or more central veins. Although it is now accepted that there is no evidence of vascular thrombosis as the basis of plaque formation, it has been suggested that local susceptibility may be particularly great in regions situated in the boundary zones between the territories of supply of major cerebral

arteries.[12] Fan-shaped lesions in the spinal cord have been described by Oppenheimer,[15] who suggests that mechanical stress, induced by repeated minor injury during neck flexion, may predispose the cervical cord to plaque formation.

In summary, it must be emphasised that all white matter is susceptible in multiple sclerosis, but for unknown reasons certain anatomical sites are more constantly damaged. The relationship of plaques to veins seems to be significant and the possibility that endothelium is primarily involved in the multiple sclerosis lesion is supported by the occurrence of increased pinocytosis in the acute lesion and by similar perivenular inflammatory lesions in the retina, a non-myelinated structure in the human. Despite very extensive study of early lesions in multiple sclerosis, there is no consensus view as to the earliest phase of myelin damage and its relationship to the inflammatory response. It seems likely, however, that subsequent events are complicated by secondary release of enzymes, complement and cytokines, and in the established lesion several patterns of tissue destruction may be seen. The perivascular position of many plaques has led to speculation that the myelinotoxic factors, known to be present in the serum of multiple sclerosis patients,[110] could be responsible for demyelinating activity, but there is no proof of this. Although there is evidence of the possible importance of immune-competent and antigen-presenting cells in demyelination in multiple sclerosis, there can be no firm conclusion that the disease is 'autoimmune'. Tissue immunohistochemistry has not established a uniform pattern of cellular reaction and the exact relationship of immune-competent cells to the elevated immunoglobulin in the cerebrospinal fluid is unknown.

The fact that diffuse astrocytosis is observed in the macroscopically-normal white matter, even in those cases which are predominantly spinal, could be interpreted as supportive evidence for primary involvement of astrocytes in the pathological response, though it must be conceded that such an effect may be non-specific. The involvement of retinal veins in multiple sclerosis suggests that myelin may not be the primary target and future studies should concentrate on early endothelial

reactions using structural, biochemical and immune techniques.

Mechanisms of lesion growth

The eventual shape and size of chronic plaques probably depends on several factors, two of which may be coalescence of adjacent lesions and finger-like extensions (Dawson's fingers) from the plaque edge. Although the coalescence of adjacent, expanding plaques can easily be understood, the mechanisms responsible for growth by extension at the periphery remain uncertain. Among several factors which could be involved at this site are the increased levels of lysosomal enzymes and the degree and extent of inflammation. For example, lysosomal enzyme levels are known to be elevated in the periplaque, rendering it potentially more vulnerable to further attack. Moreover, the cellular inflammatory response is more prominent towards the edge of old plaques, the centre of which may be hypocellular and appear inactive. Thus, the presence of perivascular inflammation at the plaque edge may mean that a continuous inflammatory process takes place, inducing further demyelination. Brosnan et al[111] have suggested that the common mechanism of lymphokine activation of macrophages will lead to release of products such as neutral proteases and these, in the presence of plasma proteins (plasminogen and complement), could cause myelinolysis. Selmaj & Raine[32] have proposed that the cytokines alpha tumour necrosis factor (αTNF) and lymphotoxin (βTNF), secreted respectively by activated macrophages and activated T lymphocytes, could be involved in the progression of the multiple sclerosis lesion through their effects on ionic channels in oligodendrocytes, myelin and axons. They reported that recombinant human TNF, when applied to myelinated cultures of mouse spinal cord causes a sequence of changes comprising oligodendroglial necrosis, irreversible myelin swelling of characteristic morphology, and eventual demyelination.

Overall significance of the neuropathology of multiple sclerosis

Many years of study have established accurate