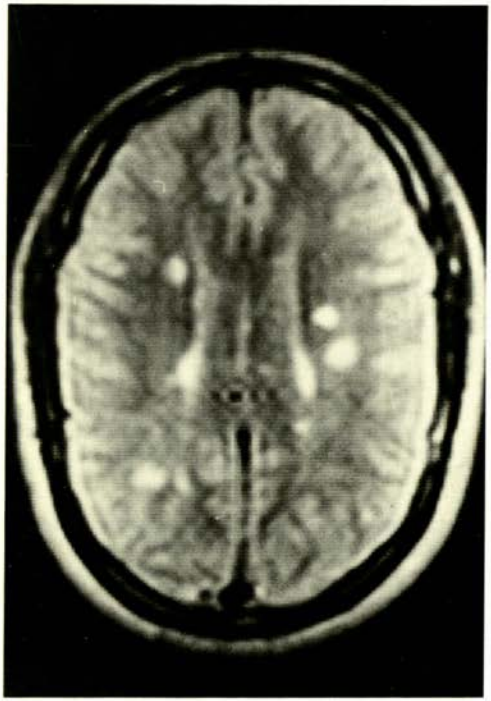
MULTIPLE SCLEROSIS



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Cover illustration: Magnetic Resonance Imaging of multiple sclerosis lesions. The scan is from a man presenting with optic neuritis but no other symptoms. Lesions are clearly visible as white patches towards the centre of the scan.

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Introduction

Multiple Sclerosis (MS) is a chronic disabling disease which attacks the central nervous system. It claims nearly a thousand lives a year in England and Wales and is responsible for an estimated 92,000 bed-days in NHS hospitals in England. In the primary care sector, general practitioners experience some 228,000 consultations annually for MS. The precise prevalence of the disease is difficult to determine but estimates range from 50,000 to 100,000 people suffering from MS in the UK. It is a disease of unknown cause, the prognosis of which is uncertain and for which there is no effective cure. In short, it is a medical mystery.

This paper reviews a number of aspects of multiple sclerosis – the definition, diagnosis, epidemiology, cost and management of the disease. The aim is to build up a comprehensive picture of MS and its consequences and identify areas where clues to causation and treatment have arisen. Certain themes, such as the geographical distribution of MS, were covered more comprehensively in the earlier OHE publication (OHE, 1975); the focus here is on other aspects of the disease and on advances and issues that have occurred in MS since the earlier paper.

The main part of this paper documents the distribution of mortality and morbidity attributable to MS and examines the health service consequences of the disease in terms of resource utilisation in hospitals and General Practitioner consultations. Thus a 'burden of illness' calculus is developed for MS based on the NHS consequences of the disease.

In section 2, the history and definition of MS is examined as a preliminary to review of the problems in diagnosing the disease and also the great uncertainty that still surrounds the prognosis for the MS sufferer. One of the diagnostic advances examined is the use of new health technologies such as Magnetic Resonance Imaging (MRI) which helps to determine those at risk of developing MS.

In sections 3 to 5 epidemiological data are analysed and the evidence on mortality and morbidity is discussed in the context of the existing literature on MS epidemiology.

In section 6, discussion focuses on the management of MS and on advances and prospects for effective treatment. In the assessment of treatment effectiveness, a contrast is drawn between the rigorous scientific evidence demanded by the medical profession from controlled clinical trials and the willingness of patients to accept very limited evidence and to try new treatments which offer some hope of cure or remission.

In section 7, health service utilisation measures for the MS disease group are costed to provide an estimate of the cost of the disease to the health service. In addition to health service costs, the high personal and family costs of the disease are examined. Very little routine published data are available on this latter topic but the clear indication is that for disabling diseases such as MS the burden of illness – financial and otherwise – is likely to fall more on the individual and his or her family than on the NHS or other state agencies.

In conclusion, section 8 draws together some of the themes arising and speculates on where the future may lead.

What is multiple sclerosis?

The French neurologist Jean Charcot is generally credited with having first identified multiple sclerosis as a disease in the 1860s, although earlier in the century the French physician Cruveihier and Scottish pathologist Carslake had devoted some attention to the condition. Working at Salpêtrière in Paris, Charcot carefully documented the signs and symptoms of the disease in patients and related these to pathological analysis of the central nervous system after death. (Charcot, 1868).

As Matthews (1980) explains, Charcot called this new disease 'sclérose en plaques' (which it remains today in the French) and the name indicates how multiple patches (plaques) of hardening (sclerosis) appear in the central nervous system. In Britain the disease was originally known as 'disseminated sclerosis' until the popular American usage of multiple sclerosis was imported and became the standard label.

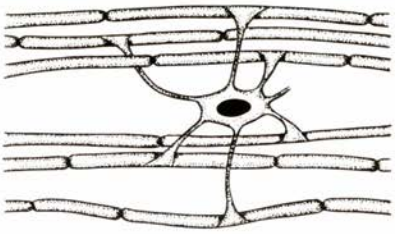
A necessary pre-requisite to discussing multiple sclerosis (MS) in any detail, is a brief description of the workings of the central nervous system (CNS) which links the brain with the outside world. The CNS performs a number of functions, channelling sensory and other information to and from the brain. To 'tell' the body to walk or talk the brain must send impulses or signals through the central and peripheral nervous systems. The nervous system itself is a series of millions of neurones or nerve cells linked together. Each nerve cell (neurone) has a cell body and a nerve fibre (axon). The axon in any one cell is important because this is the link in the chain between other nerve cells. If the chain is broken or corrupted then messages from the brain to the body may be severed or distorted.

The axons (nerve fibres) are of differing diameter – but the largest is only about one fiftieth of a millimetre. These axons are surrounded by a protective sheath known as myelin, which is a chemical compound of protein and fat. The myelin is wrapped around the nerve fibre in a spiral fashion with small gaps or nodes. In appearance the myelin is therefore segmented in much the same way as railway carriages on a train.

There are a number of other cells in the nervous system which have supporting activities. One group – known as the oligodendrocytes – are responsible for producing and maintaining the protective myelin sheath around the nerve fibres. Perhaps the simplest way to summarise this description is by reference to Figure 1.

The protective myelin sheath is analogous to insulation surrounding an electrical wire in a home appliance. Indeed a parallel can be drawn between the nervous system and a busy telephone exchange – each cable carrying unique electrical impulses but with cables carefully insulated to avoid lines becoming 'crossed' or contaminated. But in the nervous system, the myelin sheath also influences the speed at which impulses travel along the axon and it would appear to have a more complex role than simply that of protection.

Figure 1 **Diagram of nerve fibres showing myelin sheath and oligodendrocytes.**



Note Axons (nerve fibres), running left to right in the diagram are protected by a segmented myelin sheath. This sheath is maintained by 'supportive' cells such as oligodendrocytes – as in the centre of the diagram. It is the myelin sheath which is attacked and removed by MS causing problems in the transmission of nerve impulses along the axons to the remainder of the central and peripheral nervous systems.

The MS disease process is first recognised from the results of its attacks on the myelin sheath – the cause of which is unknown. The protective myelin is removed as a plaque forms. This primary process of demyelination and the formation of plaques or lesions initially appears to do no damage to the axons – it merely leaves them exposed. White blood cells (lymphocytes) cluster around the plaque and swelling occurs. It is not known why the myelin breaks down but the fact that it appears not to 'grow back' suggests that the oligodendrocytes (responsible for maintenance) are destroyed early on in the process.

The exposed axon can still function normally for a time but after a while the chronic plaques on the scarred area result in axons finally degenerating or disappearing. The process of demyelination will tend to slow down conduction of impulses along the axon, the nervous system will become severely defective because the transmission of rapid impulses (important for normal functioning) will become impaired. If axons become severed they may grow back again, but the original connections are never re-established. In terms of the earlier analogy, some 'wires' become permanently 'crossed' leaving life-long damage and symptoms.

The plaques or lesions of sclerosis are multiple in space – being scattered throughout the CNS – and in time, as the disease progresses with a continuous spread of lesions over 20 years or more. Furthermore these multiple lesions are confined to the *central* rather than the peripheral nervous system: in the latter the myelin sheaths are of a different chemical compound.

Signs and symptoms

Since the plaques or lesions can form in any part of the CNS, the initial symptoms of MS vary in type, location and severity. There are however, some sites which are more common than others; for example, the optic nerves. McDonald and Siberburg (1986, p6) note that optic neuritis (inflammation of the optic nerve) in adults '. . . is one of the commonest manifestations of demyelinating disease'. Furthermore, Shibasaki *et al* (1981) conclude that optic neuritis is the presenting feature in 20 per cent of MS cases and at some stage during the illness in about 75 per cent of cases. The axons carrying impulses from the eye to the brain often lose their myelin sheaths in such an attack. The resulting symptom is a blurring of vision, usually only in the one eye, but the severity ranges from mild blurring to complete blindness.

Visual impairment typically worsens over a period of a week or two, persists for 3 to 4 weeks and then resolves over a period of 3 to 4 months. Such attacks of optic neuritis demonstrate the peculiarly 'multi-phasic' nature of MS and the common pattern of *relapse* and *remission* over time. This is one of the most distinctive features of the disease in the majority of cases. As Matthews (1980) states '. . . the recovery is a characteristic example of that remarkable phenomenon in MS, the *remission*; a term that means substantial or complete recovery from the effects of an initial attack or subsequent relapse of the disease.'

A second common site for an initial attack is for lesions to occur in the spinal cord, resulting in 'weakness' in the legs or arms. Alternatively there may be numbness in the feet, gradually ascending to the waist. Because the spinal cord is also involved in reflexes controlling the bladder and bowel these may also be disrupted – particularly late on in the disease. Shibasaki *et al* (1981) note that symptoms suggesting lesions in the spinal cord are the presenting feature in at least a third of MS patients

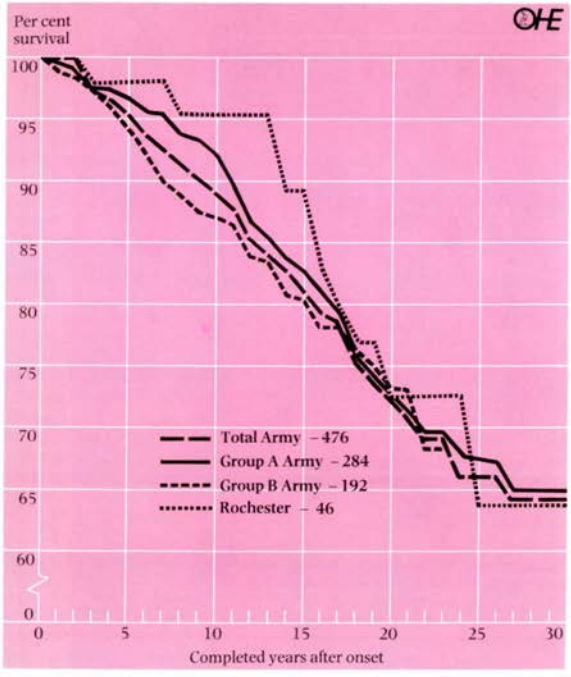
Thirdly, plaques may initially form in the brain stem or cerebellum, located at the back of the head and where all information from sensory systems is processed to regulate movement. If this is the site of the initial (or subsequent) attack the result is loss of control of movement with limbs becoming uncoordinated or ataxic giving rise to clumsiness or unsteadiness in walking and movement. Symptoms of brain stem lesions such as vertigo, diplopia and trigeminal neuralgia are the presenting feature in about 15 per cent of MS cases and occur at some stage in the course of the disease in the majority of patients (Shibasaki *et al*, 1981).

Even if the initial symptoms suggest spinal cord or brain stem lesions the timing pattern of the initial attack is often similar to that of optic neuritis with relapse and remission – attack and recovery – over a period of a month or so. Yet for the disease to be multiple (disseminated) sclerosis there must be evidence of lesions on multiple sites in the CNS; hence the diagnosing clinician is looking for evidence of the symptoms discussed above in *combination* over time.

Natural history and prognosis

In the absence of any prospective cohort study of MS patients it is diffi-

Figure 2



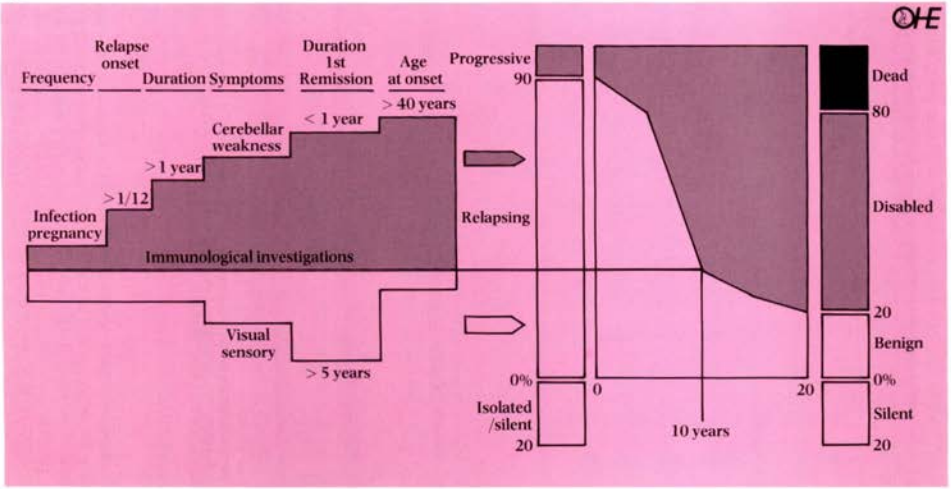
Percentage survival in multiple sclerosis from life-table analysis. Army World War II series: total; Group A, onset bout antedating Army diagnostic bout; Group B, Army diagnosis during onset bout; and Rochester, Minnesota, resident series.

Source Kurtzke (1970).

cult to document the precise development of the disease from onset. The existing evidence is the product of a variety of epidemiological methods and experience from clinical practice. Using these data however, it is possible to construct a time-profile of the manifestations of the disease from time of onset both in terms of expected disability and survival.

The most common pattern for the disease in 90 per cent of patients is

Figure 3



A diagram to illustrate the course and disability in MS; the central vertical column shows the percentage of patients presenting with relapsing or progressive disease and the right-hand vertical column illustrates the predicted outcome at 20 years. In between are actuarial curves for mortality (blackened areas) and disability (dark hatching). A vertical line is drawn at 10 years showing the decrease in slope of the disability curve thereafter. The horizontal line intercepting this is drawn to illustrate the relative weighting of clinical characteristics during the earlier (relapsing) course which can be used to predict prognosis. The height of the columns above this line in the left half of the diagram represents factors favouring a poor prognosis and the height below this line illustrates those carrying a good prognosis. *Source* Compston (1987).

the multi-phasic sequence of relapse and remission, the remainder experience the disease in its progressive form from onset. In a few cases the remission from the initial attack may be completed and the individual may experience no further symptoms. Compston (1987) estimates however, that about 60 per cent of relapse-remitting cases will switch from relapsing to a progressive course at some stage in the disease. The question is whether it is possible to predict the course of the disease in particular patient groups on the basis of initial symptoms experienced.

The impact of MS on life expectancy is difficult to determine accurately due to the problems of achieving a definitive diagnosis and hence an accurate time of onset. Kurtzke (1970), using data from the US veterans series has calculated percentage survival from onset of MS; his life table analysis is reproduced here as Figure 2. Kurtzke estimates that among these groups the median survival time was about 35 years from onset and that in the Rochester series half the survivors were still ambulatory after 20 years of illness. Other estimates of median survival time suggest that this estimate may be slightly generous (although comparisons are difficult to make), for example, 21 years (Kurland and Westland, 1954); 20–25 years (Poeck and Markus, 1974); 30 years (Hyllested, 1961) and over 21 years (Stazio *et al.* 1964).

More recently, Compston (1987) has addressed the issue of predicting the course of the disease in terms of survival and disability. Compston's prognosis model is illustrated in Figure 3, and examines expected outcomes (and potential predictors) over a twenty-year period from initial onset. Thus in 10 per cent of sufferers the disease will be progressive from onset resulting in gradually increasing disability, but in the vast majority the typical pattern of relapse and remission will be observed. It is this distinctive feature of multiple lesions occurring in time and space (ie, more than one site in the CNS) which distinguishes multiple sclerosis from other diseases of the CNS.

Although 90 per cent of cases follow a relapse-remission pattern, the majority will, at some stage, develop the progressive form of the disease. The slope of the curve on the right-hand side of Figure 3 illustrates the typical time pattern of transition from the relapsing to the progressive form of the disease with its attendant disablity. Approximately 10 per cent of cases experience frequent early relapses followed by partial remission resulting in early disability and death. Overall however, Compston puts the 20 year mortality figure at 20 per cent. In addition 60 per cent of the original cohort will be 'disabled' at 20 years. Finally, 20 per cent of patients 20 years from first onset/symptoms may have no disability because the disease has remained benign; thus an individual may only have one attack followed by remission then no other symptoms or manifestations of the disease.

More curious still is the fact that some individuals may have MS but it remains 'silent' within them. Expressed in a different way, individuals may have some medical *impairment* (lesions consistent with MS) but for some reason this impairment does not result in any apparent symptom or *disability*. This is reported to be the case in 20 per cent of individuals who, pathologically 'have' (or did have) MS, (Stazio *et al.* 1964).

Compston (1987) also addressed the question of the extent to which prognostic indicators are available and Figure 3 highlights some indicators and their predictive power. The number and frequency of relapses appears not to influence significantly the course of the disease although the rate of onset and the duration of relapse have an impact. Similarly the length of the first remission is related to the course of the disease: if the first remission is greater than five years the prognosis is favourable. The most important factor influencing the course of the disease is the age of onset; the older the individual at onset the worse the prognosis in terms of disability. (The average age of onset is in the age group 29–33 years: see the discussion of epidemiology below.)

With respect to disability, two of the main difficulties in charting the course of the disease are those of measurement and standards against which to assess physical disability. One commonly used indicator of disability is incapacity to work. In an early study Müller (1949) reported that 40 per cent of patients were incapacitated for work within 5 years from onset, 50 per cent within 10 years and 66 per cent within 15 years. Ipsen (1950) reports that 50 per cent of patients had to stop work within 5 years of onset. More recently Bauer (1965) indicates that 70 to 80 per cent of patients with MS for more than 20 years are unemployed. Scheinburg *et al* (1981) note that the main reasons cited for leaving work include spasticity, uncoordination, gait difficulties, visual disturbance, transportation difficulty and fatigue.

But work capacity is a crude indicator of disability because people have different jobs which make differing physical and mental demands upon them. The evidence suggests that those with MS who are still in employment are in white-collar managerial or professional positions which have relatively smaller manual input. Thus the extent to which similar degrees of *disability* result in the same levels of physical and social *handicap* depends upon the nature of the job and other parameters of the individual's lifestyle.

At the level of physiological functioning a more reliable measure of disability is achieved through the categorisation of disability levels to achieve an index measure such as the Disability Status Scale developed by Kurtzke (1961). The scale ranges from 0 (normal neurological examination) to 10 (death due to MS). Such measures are of value not only for charting the disability course of the disease but also in the assessment of competing therapies for MS in clinical trials. The use of Kurtzke scales in clinical trials is discussed in the section on assessment of treatment later.

Diagnosis

The *definitive* diagnosis of MS can only be made with the pathological evidence from a *post mortem*. During a person's lifetime the lesions are locked away in the Central Nervous System making examination of them extremely difficult. For practical purposes however, it is necessary and possible to undertake a clinical diagnosis for patients using the available evidence on signs and symptoms in conjunction with paraclinical investigations such as imaging.

The most recent diagnostic criteria are those of the Poser Committee (Poser *et al*, 1983). This Committee, acknowledging the uncertainty still surrounding clinical diagnosis of MS, distinguish between two groups of cases – *definite* and *probable* MS – each with two subgroups of *clinical* and *laboratory supported*. The Poser criteria are reproduced here in Box 1.

Box 1 *The Poser Committee Diagnostic Criteria for MS (Poser* et al *1983)*

1 **Clinically definite multiple sclerosis**

(a) Two attacks and clinical evidence of two separate lesions.

(b) Two attacks, clinical evidence of one and paraclinical evidence of another separate lesion.

2 **Laboratory-supported definite multiple sclerosis**

(a) Two attacks, either clinical or paraclinical evidence of one lesion and cerebrospinal fluid oligoclonal bands.

(b) One attack, clinical evidence of two separate lesions and cerebrospinal fluid oligoclonal bands.

(c) One attack, clinical evidence of one and paraclinical evidence of another separate lesion, and cerebrospinal fluid oligoclonal bands.

3 **Clinically probable multiple sclerosis**

(a) Two attacks and clinical evidence of one lesion.

(b) One attack and clinical evidence of two separate lesions.

(c) One attack, clinical evidence of one lesion and paraclinical evidence of another, separate lesion.

4 **Laboratory-supported probable multiple sclerosis**

(a) Two attacks and CSF oligoclonal bands.

Note An 'attack' is the occurrence of a symptom or symptoms of neurological dysfunction which lasts for more than 24 hours.

For a clinically definite diagnosis of MS there must ideally be evidence of two attacks on different parts of the CNS, each lasting more than 24 hours and separated by a period of at least one month. Hence, there must be evidence that lesions are multiple (disseminated) in both time and space. Clinical evidence of lesions can be complemented with paraclinical evidence from electrophysiological procedures such as evoked potential tests and also by imaging procedures such as CT scanning and magnetic resonance imaging (MRI). In addition to clinical and paraclinical evidence there may also be laboratory support to a diagnosis of MS obtained from examination of cerebrospinal fluid (CSF) which may indicate immunological abnormality.

Advances in the ability to diagnose MS more accurately are constantly being achieved as scientific and medical technology pushes forward. The lumbar puncture, for example, has been a diagnostic aid for a number of years, and is a means of extracting some of the cerebrospinal fluid (CSF) which surrounds the CNS for laboratory analysis. A sample of CSF is withdrawn by use of a fine needle inserted between two of the lumbar vertebrae in the lower back. The CSF will be abnormal in about 50 per cent of MS sufferers and one such abnormality is a high concentration of protein in the CSF (Lumsden, 1972). More specifically, MS patients tend to have high levels of immuno gamma globulin (IgG) in the CSF (Lumsden, 1972) As well as being a diagnostic advance, the relationship between gamma globulin and their role in the formation of antibodies suggests that the cause of the disease in part or in whole is immunological.

Another group of diagnostic aids determine whether demyelination has occurred by measuring the speed at which nerve impulses are transmitted from (say) the eye to the brain. Since the myelin not only protects the axon but also aids conduction of impulses it should be possible to detect occurrences of demyelination. Such tests are termed Evoked Potential tests and a common example is the Visual Evoked Potential (VEP). Normally the time from visual stimulus to response is 100 milliseconds but after a demyelinating attack of optic neuritis this response time would be delayed. Furthermore, it was found that this reduced VEP could persist even after the symptoms of optic neuritis had subsided (Matthews, 1980, p40). There are a number of other evoked potential tests used to examine different sites on the CNS.

One of the main areas of diagnostic advancement has been in the application of radiological techniques with the aim of viewing the presence or absence of multiple lesions in the brain early in the course of the disease. Computerised Axial Tomography (CT) scans became possible in the 1970s and neurologists were able to produce images of the brain and identify some of the lesions present (Warren *et al*, 1976). The accuracy with which CT scans can be interpreted, however, depends upon the density and size of the lesions – essentially the contrast they make against the surrounding matter. A more sophisticated instrument – Magnetic Resonance Imaging (MRI) – has recently been developed which essentially renders CT scanning technically obsolete.

Matthews (1985) explains how MRI of the brain can be used in the detection of MS.

> 'This method depends on the excitation of hydrogen nuclei by radio frequency radiation. Grey matter contains more water than white matter and therefore more hydrogen. In the normal brain, therefore, the distinction between grey and white matter is far more obvious than in even the most advanced CT scan. Demyelinated plaques have lost much of their lipid content, replaced in part by water, and can thus be detected by MRI.'

The plate on the front cover of this paper is an illustration of MS lesions in the brain as detected by MRI, being the scan of a man who had presented with optic neuritis.

The increased accuracy of MRI over CT scanning was demonstrated by Young *et al* (1981) who examined 10 patients with MS by CT scan and found a total of 19 lesions – MRI found the same lesions and an extra 112 smaller lesions. Yet despite the accuracy of MRI the problem remains that the relationship between the presence of lesions and the development of MS is still uncertain. Individuals can have lesions and yet have no symptoms of MS in their lifetime. The dilemma is how the diagnostic clues offered by MRI can best be handled between doctor and patient. The neurologists proceed with caution. Would it be appropriate for example, to use this costly resource to scan everyone who presents with optic neuritis only to be able to tell individuals that lesions are present and that they are *at risk* of developing MS symptoms in the future?

Such a screening approach seems inappropriate because MRI forms only one component of the diagnostic process and, as the Poser criteria indicated, the primary motivation should be a clinical diagnosis based on signs and symptoms which is *supported* by paraclinical evidence from procedures such as MRI.

In summary, the diagnosis of MS remains notoriously uncertain. Difficulty in identifying the disease early may cause delay in those areas of management or treatment which may be beneficial. Diagnostic uncertainty will also tend to create problems when assessing the epidemiology of MS – its incidence and prevalence.

Theories of causation

As with any disease where the cause remains unknown there are no shortage of theories which purport to 'explain' the incidence of MS. It is not possible, in this paper, to document and discuss all the theories that have been put forward: the aim is to focus on the two main areas of discussion with respect to the causative agent behind MS. The first is that some form of viral infection provokes an auto-immune response resulting in demyelination. The second is diet – in particular the intake of animal fats. Each theory (and subsets of them) must be judged on the available evidence. To this end, the following brief outline of current thinking should be considered in the context of the chapters on both the epidemiology and the management of MS.

The intake of fat in the diet is of interest in MS because the myelin sheath is mainly fat (lipids). Dick (1976) has suggested, for example, that susceptibility to demyelination may be due to an increase in the proportion of saturated fatty acids in cerebral lipids relative to unsaturated fatty acids. The possible significance of fat intake had been investigated earlier by Swank (1950) who found a high correlation between the geographical distribution of MS and the consumption of animal fat.

The empirical evidence to support Swank's hypothesis comes mainly from a Norwegian Survey (Swank *et al*, 1952) which examined dietary intake in seven communities. Yet although the data are consistent with the view that high animal fat intake and risk of MS are correlated, Acheson (1985) comments that the epidemiological data are '. . . neither on a large enough scale nor in sufficient detail to be convincing'.

A second strand of reasoning with respect to fat intake is that there may be a fault with the way MS sufferers metabolise essential fatty acids (EFAs). In particular many MS patients have been found to have low levels of linoleic acid and this has given rise to treatment theories aimed at increasing this entity using dietary supplements such as 'evening primrose oil' which are high in linoleic acid content. Research into the possible relationship between a wide range of EFAs and MS has developed a number of complex hypotheses. Some of the evidence on these is reviewed in the section on management of MS below.

Much of the available evidence suggests that MS is some form of disease affecting the immune system which finds origin in a viral infection. There may be some genetic defect in the immune system which permits the persistence of a virus such as measles which is acquired in childhood – the virus somehow lays 'dormant' within the body. In later life the virus either directly attacks the myelin sheath or stimulates an autoimmune response to the myelin.

There are a number of strands of evidence in support of this hypothesis. Early studies tried to isolate a particular virus related to MS and found that when examining the blood and cerebrospinal fluid (CSF) of MS sufferers many of them have high concentrations of measles antibodies (Norrby, 1978). Such antibodies are the body's defences against the acute disease (measles) and usually, when the infection is over, this immune reaction ceases and antibody levels return to normal. Persistently elevated antibody levels in MS patients therefore suggests that the virus is not removed completely after the initial attack but it may be lying dormant in the body. (A common example of a persistent viral infection are cold sores due to the herpes simplex virus which remains in cells in the base of the brain in some individuals.) The evidence on this measles viral infection theory varies between individuals such that it could not be used as a definitive diagnostic test although CSF sampling for raised immunoglobulin levels does form one of the diagnostic tools for MS (see diagnosis above).

Measles may not necessarily be the infective agent responsible. The source of the virus might be animals. A naturally recurring neurological disorder among sheep is called 'scrapie' – so called because diseased sheep scrape themselves on fence posts. Early studies showed that this disorder could be transferred from one sheep to another as an infection. This raised the possibility that it could be transferred to humans and it was hypothesised that there may be a relationship between the incidence of MS and contact with sheep – for example, the high rates in places such as the Orkneys. But this has not been demonstrated to be a consistent relationship. Studies by Cook and Dowling (1977) and others have suggested that the infective agent may be canine distemper and they demonstrate a possible relationship between individuals contracting MS and contact with household pets, in particular 'neurologically ill dogs'. This however, remains a fringe theory and Acheson (1985) notes that six subsequent studies have not found such a relationship.

An important element concerning the viral infection theory of causa-

tion – whatever the source of the virus – is that there may be some genetic link. Some individuals, in addition to being exposed to an external agent, may already have an inborn or acquired vulnerability to the disease. The background to this reasoning comes again from the immunologists who found that particular HLA antigens were found more frequently in MS sufferers. The HLA system is that used for determining 'tissue match' in kidney transplants where attempts are made to match often unrelated donors and recipients on the A, B and DR antigens. Every individual has a specific 'blueprint' of HLA antigen types and these genetic blueprints would be the same for related individuals.

Certain HLA types such as DR2, have been found to be more susceptible to MS than others (Batchelor *et al*, 1978) and the incidence of MS geographically may be related to DR2 distribution (Swingler and Compston, 1986). Therefore if MS susceptibility is a function of HLA type it is logical that such susceptibility is hereditary. The difficulty with testing the hypothesis of hereditability is the fact that (say) mother and son are likely also to be exposed to the same range of external agents, such as diet, which may play a part.

Gonzalez-Scarano *et al* (1986) have recently concluded that 'Family studies strongly suggest that there is a major genetic influence upon susceptibility to MS'. But it must be stressed that the genetic link is far from 100 per cent. Genetic studies on monozygotic (identical) twins, for example, have demonstrated that no more than 30 per cent of such twins (where the other has MS) develop the disease. Such evidence suggests that although there is some genetic susceptibility there must also exist some external environmental 'trigger' to produce the disease.

In addition to epidemiology and laboratory research it may be possible to learn more about the cause of MS by examining the history of other diseases. Poliomyelitis is a possible contender, being a disease of the central nervous system caused by a particular viral infection which could result in paralysis. The virus was spread by contaminated food, water or by infected flies. A century ago it was a disease that occasionally caused paralysis in babies and infants; it was therefore called 'infantile paralysis'. At that time many infants were infected and developed immunity, but only one in several thousand developed the disease causing paralysis. However, if the individual contracted the disease for the first time as an adult then paralysis was much more likely to occur.

Therefore individuals who came from an area where good hygiene was observed (a social class, a country, or a point in time) during childhood were more likely to get the infection for the first time as an adult and result in being paralysed. This was observed with the British troops during the war in North Africa. Many troops went down with poliomyelitis but a higher proportion of the officers suffered paralysis than the other ranks. The reason was that the officers as a group came from a social class background where they were more likely to miss an early infection in childhood which would have left them immune to the disease.

One of the interesting aspects about the epidemiology of MS is that it

is distributed more towards the higher end of the social class spectrum (Russell, 1971). The UK evidence on this distribution is presented in the section on epidemiology below and such evidence is not inconsistent with reasoning similar to that concerning the nature of the polio virus and immunity by social class.

But the mystery of MS is more complex than that of polio. With the latter the viral infection agent was isolated and effective vaccines produced so that population immunity could be generated as prophylactic treatment. The problem with MS is that researchers have not, as yet, been able to isolate a specific viral infection which is responsible; although this is obviously the subject of much current research.

Epidemiology I: Data for England and Wales

There are a number of difficulties encountered when examining the epidemiology of a chronic disease of unknown origin and uncertain prognosis such as multiple sclerosis. Perhaps the central focus of concern is the problem of consistency in the identification and diagnosis of MS. At one level, it is simple to classify MS: it is a disease of the central nervous system with the code number ICD 340 in the ninth revision of WHO's International Classification of Diseases. Yet to build up an accurate picture of the distribution of mortality and morbidity using published data on this disease classification it is important, first of all, critically to assess how the published data can best be interpreted.

The first problem with respect to morbidity is the reliability with which cases are diagnosed as being MS. Since there is no single (*ante mortem*) definitive diagnostic test for MS, the reliability of case identification will vary and will be a function of both clinical experience with the disease (recognising symptoms) and the availability of more sophisticated laboratory tests. The extent to which cases are undetected is difficult to determine but one study estimated that as many as 20 per cent of cases are not detected during life (Stazio *et al*, 1964).

Mortality data are generally a more reliable epidemiological indicator than morbidity. However, the problem with chronic diseases such as MS is that often it is the acute (immediate) cause of death which is recorded on the death certificate rather than the long-standing illness. Matthews (1985, p61) for example, notes that 'In chronic multiple sclerosis, pneumonia, septicaemia from pyelonephritis and sepsis and loss of protein from bedsores are the usual cause of death'. The majority of MS patients therefore die of manifestations of the illness such as infections consequent upon their paralysed state, and not of the disease *per se*. One study by Shepherd (1976) estimated that for this reason MS mortality could be underestimated by up to 50 per cent.

When examining the morbidity attributable to MS it is important to distinguish which of the available data relate to the *incidence* and which to the *prevalence* of the disease. Health care utilisation measures such as new GP consultations or hospital admissions are likely to be an indica-

tion of the former but not the latter. Incidence indicators reflect the frequency of *new episodes* of the disease occurring. Prevalence, on the other hand, is more difficult to determine from utilisation data because it is an indicator of the existing 'stock' of the disease in the community – the number of cases existing at a given point in time. Undue dependence upon either of these measures in isolation may give a misleading picture of a chronic disease such as MS. The incidence of a disease can remain constant while the prevalence is increasing, simply due to the fact that survival of patients is improving.

Mortality

Mortality data on MS in England and Wales are presented in Table 1. Thus in 1985 there were a total of 938 MS deaths recorded, a figure which accounts for 0.16 of one per cent of all mortality in that year. Nearly two-thirds of total MS mortality (603) were females, and mortality numbers peak in the 55 to 64 year age group.

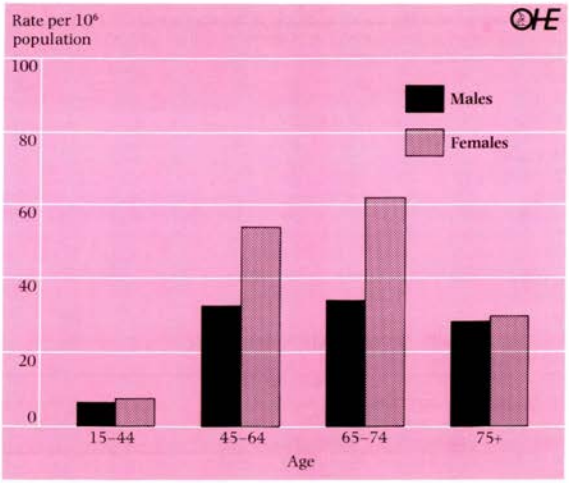
Age and sex-specific MS mortality rates per 10 million population are illustrated in Figure 4. These population standardised data suggest that

Table 1 **Mortality from multiple sclerosis (ICD 340) by age and sex, England and Wales 1985**

Age		*Mortality all causes*	*Mortality: multiple sclerosis*	*Percentage of all mortality due to multiple sclerosis*
Under 15:	M	4,979	—	—
	F	3,696	—	—
15–24:	M	3,112	1	0.03
	F	1,174	1	0.03
25–34:	M	2,953	10	0.34
	F	1,583	24	1.52
35–44:	M	5,776	56	0.97
	F	3,803	60	1.58
45–54:	M	14,383	61	0.41
	F	9,111	115	1.26
55–64:	M	45,704	112	0.25
	F	27,664	186	0.67
65–74:	M	85,695	65	0.08
	F	59,285	153	0.26
75+:	M	129,270	30	0.02
	F	192,091	64	0.03
All Ages:	M	292,327	335	0.11
	F	298,407	603	0.20
	P	590,734	938	0.16

Source OPCS (1986), *Mortality cause*.

Figure 4 **Age and sex-specific mortality rates per million population for multiple sclerosis: England and Wales 1985.**



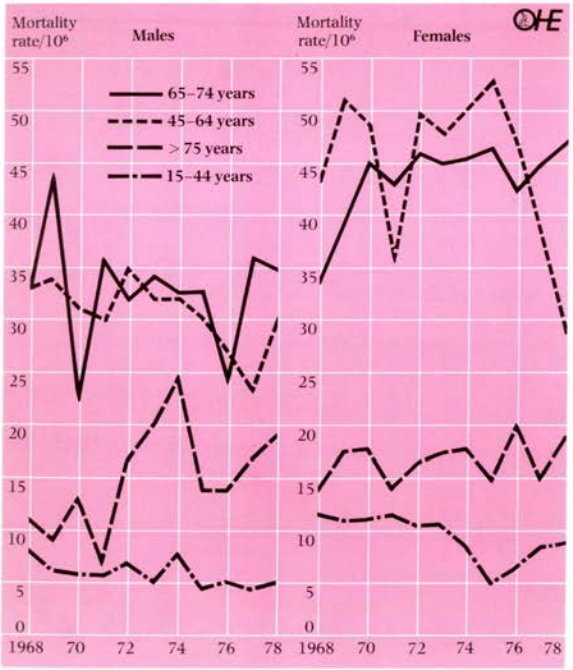
Source OPCS (1986) Mortality: cause.

mortality rates are highest in the 65 to 74 age group (62.2 per million) for females and males (33.6 per million). It is also in this age group where the sex ratio in mortality rates is most marked, being nearly twice as many females as males.

Male and female age-specific mortality rates over time are presented in Figure 5. Swingler and Compston (1986) report that there has been a significant decline in mortality for males aged 45–64 years and females aged 15–44 years, although there are increasing rates in older age groups over time.

The geographical distribution of mortality within the United Kingdom is detailed in Figure 6 in the form of standardised mortality ratios (SMRs). The most distinctive feature of this comparison is that Scotland has a much higher rate of MS mortality (given its age-sex distribution) than other areas of the United Kingdom. Yet the picture is not a simple North-South divide. Health Regions such as South West Thames have SMRs in excess of 100. To some extent however, this latter observation may be a statistical artefact due to the hospital mortality of patients who migrate towards London teaching hospitals to undergo some of the more sophisticated treatment or neurological investigations.

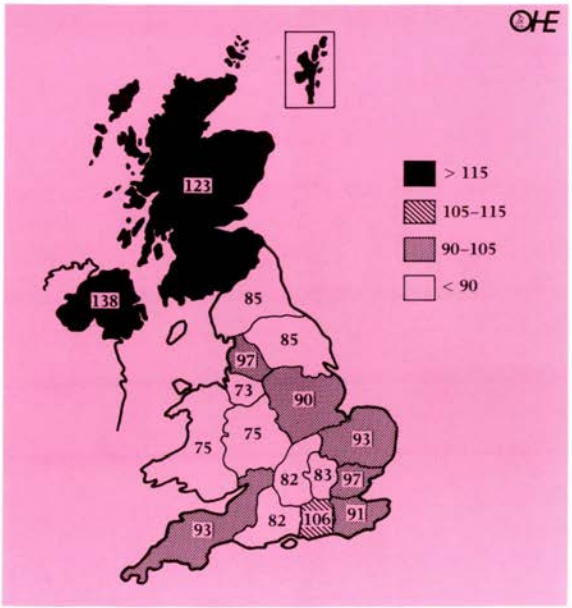
Figure 5 **Change in MS mortality over time by age and sex: England and Wales 1968–78.**



Source Swingler and Compston (1986).

One of the intriguing aspects of MS mortality is its distribution across social class groups. An early study of MS incidence by Russell (1971) found significantly more patients were from Registrar General's social classes I and II, holding professional and managerial jobs, than would be expected on the basis of population statistics. The decennial supplement on mortality by occupational groups for 1982/83 has recently been published by OPCS (OPCS, 1986). This details mortality by cause within the five social class groupings of the Registrar General which are based on occupation. These data are illustrated in Figure 7 in the form of standardised mortality rates (SMRs) and proportional mortality rates

Figure 6 **Standardised mortality ratios (SMRs) for multiple sclerosis by Health Authority Regions 1976–80.**



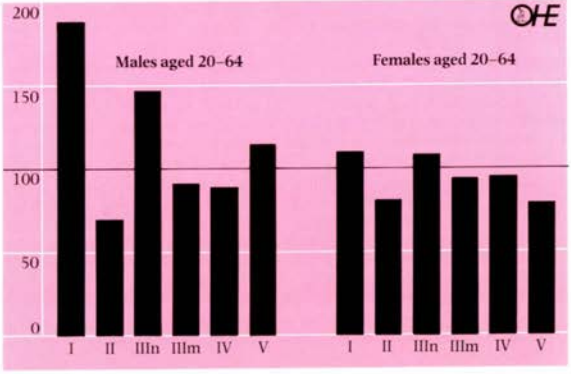
Source Swingler and Compston (1986).

(PMRs). There would seem to be a marked gradient in MS mortality across social class groups, being higher in social class I than V. Figure 7 indicates that this pattern is more consistent for females and more marked for those in the 65–74 age group. In that age group females in social class I are nearly six times more at risk of MS mortality than those from class V.

Morbidity

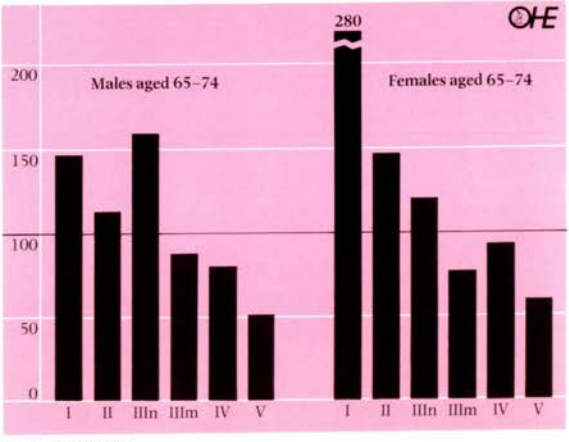
The popularity of mortality rates in epidemiology is due largely to the fact that death certification remains one of the more reliable epidemiological observations. Yet it is generally accepted that mortality data, especially for chronic diseases, is often a poor proxy for the number of people in the population suffering from a given disease.

Figure 7a **Multiple sclerosis mortality by social class: Great Britain 1982/83: Standardised mortality ratios.**



Note Social class according to Registrar General's classification of occupation.
Source OPCS, occupational mortality 1982/83 (1986).

Figure 7b **Multiple sclerosis mortality by social class: Great Britain 1982/83: proportional mortality ratios.**



Source OPCS (1986).

There are two basic approaches that can be adopted when attempting to form estimates of morbidity in a population. The first is to launch a detailed survey of sickness or disability such as that mounted by Amelia Harris and colleagues (1971). The second is to rely on the routine national data sources which detail health care utilisation in its many forms. There are strengths and weaknesses in both approaches. The survey approach will provide a useful guide to the *prevalence* of a given disease as found on the day of survey. In contrast health care utilisation measures give some indication about new episodes arising, the *incidence* of the disease and some limited indication of prevalence.

The 1971 study by Harris and colleagues was designed to provide estimates of the number of handicapped people aged 16 and over living in private households in Great Britain. Those surveyed were categorised by degree of handicap, with handicap ranging from 'very severe' to 'appreciable'. The survey showed that in 1968 there were just over 18,000 persons with MS living at home who were appreciably handicapped. In many individuals diagnosed as having MS the disease may not produce any handicap until later in life, although symptoms may be present. Therefore the overall numbers of MS victims in the population were thought to be in the region of 40 to 50,000.

A specific survey of disability by the Office of Population Censuses and Surveys (OPCS) is due to be published in late 1987 and will provide updated evidence of the prevalence of disability in society as a whole and will enable some identification of MS within this burden. However, it is possible to update epidemiological knowledge by using some of the data sets available on health care utilisation. The following reports on two basic areas of hospital care and primary care utilisation by MS patients.

Hosptial inpatient care

The Hospital Inpatient Enquiry (HIPE) is an annual sample survey of patients in hospital in England. Data are collected on every tenth patient discharged from hospitals in England. Details on the age and sex-specific discharge rates per MS per 100,000 population are presented in Table 2 and illustrated in Figure 8.

As with mortality, discharge rates from hospital indicate a higher rate of MS morbidity for females relative to males in all age groups. The 'peak' of the hospital care distribution for MS patients appears to be in the 45–64 age group and this is also the group where the sex ratio is most marked being a rate of 43.4 per 100,000 for females and 26.8 for males.

In Figure 9 hospital discharge rates are presented by Regional Health Authority (RHA) as proportions of the mean discharge rate. Analysed in this way, hospital activity on MS yields a similar geographical distribution to that of mortality with high activity rates in Scotland and clustered around the Thames regions.

Morbidity estimates from general practice studies

The third National Morbidity Survey by the Royal College of General

Table 2 **Hospital in-patient days per annum for multiple sclerosis (ICD 340), England 1984**

Age		Estimated deaths and discharges	Mean length of stay	Median length of stay	Total bed days high estimate	Total bed days low estimate
0–4:	M	—	—			
	F	—	—			
5–14:	M	—	—			
	F	—	—			
15–44	M	1,430	44.6	8	63,778	11,440
	F	2,370	53.7	8	127,269	18,960
45–64:	M	1,370	48.0	10	65,760	13,700
	F	2,290	83.4	13	190,986	29,770
65–74:	M	330	35.3	14	11,649	4,620
	F	460	81.9	18	37,674	8,280
75–84:	M	50	41.6	14	2,080	700
	F	190	52.6	23	9,994	4,370
85 & over	M	—	—	—	—	—
	F	—	—	—	—	—
All ages:	M	3,180			143,267	30,460
	F	5,310			365,923	61,380
	P	8,490			509,190	91,840

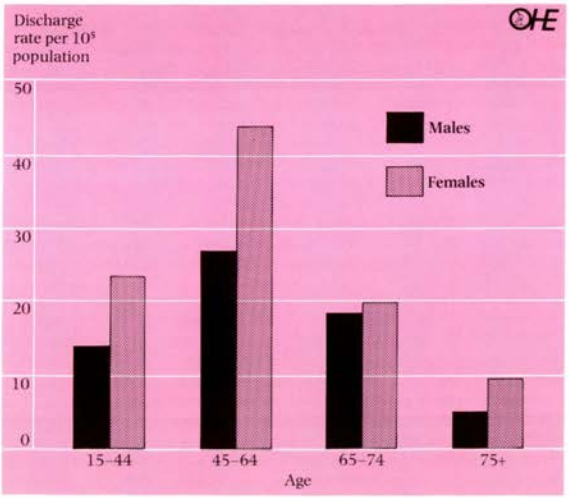
Source Hospital Inpatient Enquiry.

Practitioners (RCGP) has recently been published and relates to data collected from general practice in England and Wales in 1981/82. Details on the age and sex of patients consulting due to multiple sclerosis are presented in Table 3.

One measure of the incidence of MS is the number of new consultations per 1,000 population for the disease in the survey period. The overall incidence rates were 0.1 per 1,000 population for males and 0.2 for females. The total number of consultations for MS gives an indication of the utilisation of general practice by MS patients. Consultation rates per 1,000 population were found to be 6.0 for females and 2.9 for males. Age and sex-specific consultation rates for MS are presented in Figure 10. Female rates are consistently higher than male in all age groups. Consultation rates are highest for males in the 25–44 age group (6.1 per 1,000) and for females in the 45–64 age group (12.1 per 1,000). The biggest difference between the sexes is in the 45–64 age group where consultations for MS are nearly four times more likely to be female than male.

Because an individual patient might consult a GP more than once in a given year because of MS, consultation rates are probably more use-

Figure 8 **Age-specific hospital discharge rates per 10^5 population for multiple sclerosis: England 1984.**

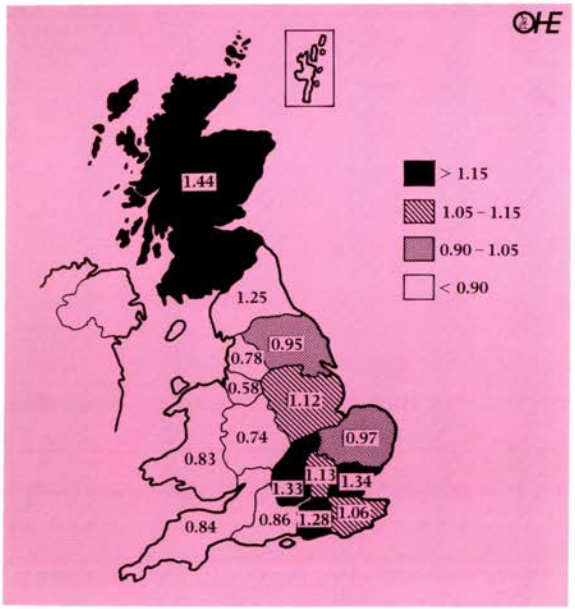


Source Hospital inpatient enquiry (1986).

ful as an indication of the source of GP workload rather than as a guide to the prevalence of the disease. Data are also presented in Table 3 on the number of patients per 1,000 population consulting for MS – these rates being 1.2 for female and 0.5 for male. In general then these sample data, when projected for 1985, would indicate that a total of about 40,000 patients consulted a GP at least once in 1985 in England and Wales because of MS.

The National Morbidity Surveys are not the only source of morbidity data from general practice. Data on patient diagnoses and pharmaceutical treatments are routinely sampled from UK general practitioners by Intercontinental Medical Statistics (IMS) for the purpose of constructing market research audits for the pharmaceutical industry. Data are collected continuously and published quarterly when quarterly and annual projections are made to estimate UK totals. Table 4 presents annual projections for MS from the twelve months to June 1986.

Figure 9 **Mean proportional hospital discharge rates for multiple sclerosis by health authority.**



Source Swingler and Compston (1986).

IMS estimate an annual total (1986/87 projection) of 487,000 GP consultations for multiple sclerosis in the UK; this being 0.11 per cent of total United Kingdom consultations. The age-sex distribution of consultations is very similar to that found by the RCGP morbidity survey with a high female/male sex ratio in all age groups above 29 years, with females accounting for nearly twice the number of male consultations.

Details of the 'place' of consultation are also collected by IMS, and these are detailed in Table 5. The majority of consultations (37.1 per cent) take place in the doctor's surgery with 31.1 per cent being home visits. A high proportion of 'consultations' (21.1 per cent) are instances where the patient is seen by the GP's receptionist. Reasons for this will include 'repeat prescribing' where the patient is merely obtaining a

Table 3 **Incidence and consultation rate per 1,000 population for multiple sclerosis (ICD 34), England and Wales 1981/2.**
Rates per 1,000 population

		Incidence	*Patients consulting*	*Consultations*	*Estimated number of consultations in 1985*
0–4:	M	—	—	—	—
	F	—	—	—	—
5–14:	M	—	—	—	—
	F	—	—	—	—
15–24	M	0.0	0.1	0.4	1,658
	F	0.1	0.2	0.5	1,992
25–44:	M	0.2	0.7	6.1	41,993
	F	0.3	1.5	9.7	65,768
45–64:	M	0.1	0.9	3.5	18,974
	F	0.3	2.5	12.1	67,594
65–74:	M	—	0.8	4.3	8,318
	F	0.3	1.8	7.6	18,706
75+	M	—	0.2	0.2	216
	F	0.1	0.4	1.3	2,806
All ages:	M	0.1	0.5	2.9	71,099
	F	0.2	1.2	6.0	156,866
	T	0.1	0.8	4.5	227,965

Source Royal College of General Practitioners (1986).
Morbidity Statistics from General Practice 1981–1982.

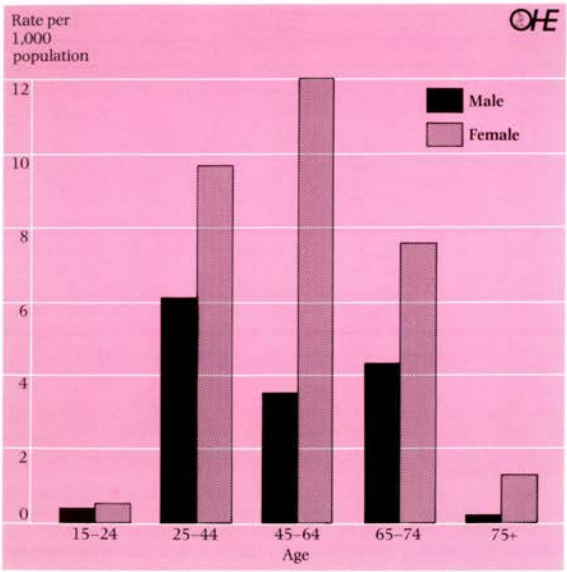
Table 4 **Estimated annual number of patients diagnosed by general practitioners as having multiple sclerosis (ICD 340), UK, 12 months to June 1986.**
Diagnosis (000's)

Age	*Male*	*Female*	*Total*	*(Percentage)*
0–19	—	—	—	
20–29	19	20	39	(8)
30–39	25	64	89	(19)
40–45	62	113	175	(36)
55–64	30	76	106	(22)
65+	21	49	70	(15)
Sub Total*	158	323	481	(100)
Not Specified			6	
Total			487	

*Due to rounding in original source, columns may not total precisely.

Source Medical Data Index – Intercontinental Medical Statistics Ltd.

Figure 10 **GP consultation rates per 1,000 population for multiple sclerosis: 1981/82, England and Wales.**



Source Royal College of General Practitioners (1986).

repeat prescription for some maintenance therapy, and also the administrative function of certification such that disability allowances can be claimed by patients. Of the remaining consultations where the place of visit was stated by the sampled GPs, 4.7 per cent were consultations over the telephone and 0.2 per cent took place in a clinic.

General practitioners in the IMS sample were also asked to record whether the consultation was a *first* visit for a diagnosis of multiple sclerosis or whether it was a *subsequent* visit. Analysing total consultations in such a way gives some indication of incidence and prevalence of the disease. The data show that 34,000 (6.9 per cent) were first visits and 420,000 (86.3 per cent) were subsequent visits. (In 33,000 cases the type of visit was not specified.) This suggests that the vast majority of GP consultations for mutliple sclerosis are for prevailing (existing)

Table 5 **Place of GP consultation for multiple sclerosis: UK, 12 months to June 1986.**

Place of consultation	*Annul number of consultations (000's)*	*Percentage*
Surgery	174	37.1
Receptionist	99	21.1
Home	145	31.1
Telephone	22	4.7
Clinic	1	0.2
Other	27	5.9
Sub Total	468	100.0
Not Specified	19	
Total	487	

Source Medical Data Index – Intercontinental Medical Statistics Ltd.

cases rather than new cases. In the National Morbidity Survey only 10 per cent of MS cases were classed as new episodes by GPs – again confirming that the majority of general practice utilisation for MS is for prevailing cases.

One further piece of IMS information relating to GP consultations for MS is that on referrals. Data are available on whether the consultation *resulted* in the GP referring the patient to hospital and whether the consultation *originated* in a referral from a hospital. Where this information had been recorded in the survey, 24,000 (6.5 per cent) consultations ended with referral to hospital and 44,000 (11.5 per cent) consultations originated from a hospital referral.

Medicines prescribed

A further indicator of morbidity for a particular disease group is the number and type of medicines prescribed for treatment. General practitioner prescribing of ethical pharmaceuticals for particular disease groups forms a large part of the IMS database previously discussed. In Table 6 data are presented on the leading pharmaceuticals prescribed in the treatment of MS in general practice. Medicine groups are defined according to the Anatomical Therapy Class (ATC) system.

An estimated total of 310,000 medicines are prescribed annually in the UK for MS. Of course, not all the consultations for MS will result in a prescription being written. IMS data indicate that less than half (44 per cent) of consultations for MS result in a prescription; in contrast, and using 1982 IMS data, O'Brien (1984) estimated that 74 per cent of all UK consultations resulted in some form of prescription being written.

Table 6 **Pharmaceuticals prescribed for mutliple sclerosis (ICD 340) in general practice, UK, 12 months to June 1986.**

		Estimated annual number of items (000)	*Per cent of all MS items*
M3	Muscle Relaxants	60	19.2
A11	Vitamins	43	13.8
N2	Analgesics	38	12.1
N5	Psycholeptics	35	11.4
H1	ACTH	27	8.8
G4	Urologicals	15	4.9
A6	Laxatives	12	3.9
A4	Antiemetics/Antinauseants	9	2.9
C3	Diuretics	9	2.9
N3	Anti-Epileptics	7	2.3
D8	Antiseptics, disinfectants	7	2.2
N6	Psychoanaleptics	6	2.0
H2	Systemic Corticosteroids	5	1.6
O2	Emollients and protectives	4	1.3
C7	Beta Blocking Agents	4	1.3
A3	GI Antispas., Anticholinerg	4	1.3
	All other drugs	25	8.1
	Total	310	100.0

Source Medical Data Index – Intercontinental Medical Statistics Ltd.

(Again, this may be due to high proportion of consultations being 'administrative' – certification for benefit claiming.) Therefore, only 215,000 of the total 487,000 consultations are 'treated' by prescription medicines and on average each of these treated patients will receive 1.45 prescription items. (Obviously items per patient will vary between patients on the basis of age, sex, and other variables.)

Epidemiology II: International comparisons

Large variation in the world-wide distribution of MS is the one aspect of the disease, perhaps more than any other, which has engaged the minds of epidemiologists over the years. The challenge facing epidemiologists is to try to relate environmental, genetic and other predisposing factors to the international differences in the prevalence of the disease. In this section only the world-wide patterns of distribution will be presented – theories concerning the possible reasons behind differential rates will be discussed later.

One of the immediate problems which arises when attempting to make international comparisons of disease prevalence is that different accounting techniques are used – prevalence is not always and everywhere measured in the same way or with the same degree of accuracy. A researcher who has made great contributions in this area is John Kurtzke. Over a number of years working in this area Kurtzke has catalogued and reviewed a number of surveys of MS and recalculated prevalence according to a standard practice. (For example, see Kurtzke 1975; 1980.)

Limburg's hypothesis

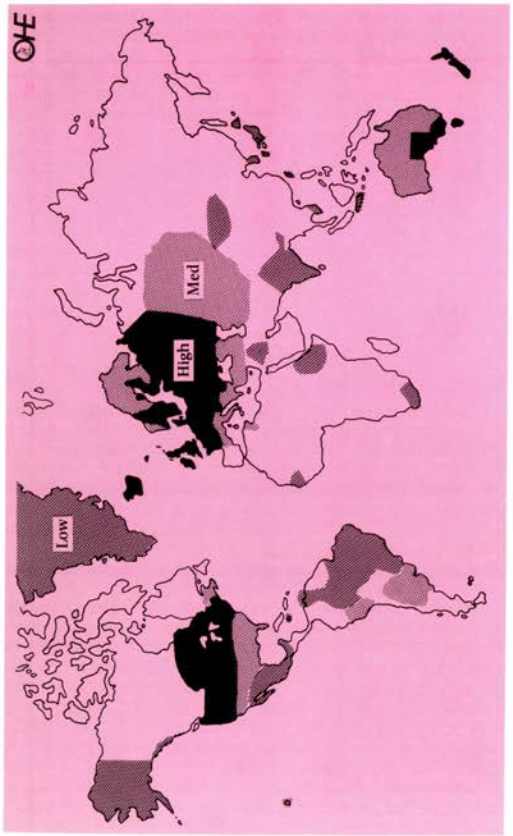
The more recent studies on geographical distribution have been generally consistent with the hypothesis put forward by Limburg (1950) that the frequency of multiple sclerosis increases with distance from the equator in both the northern and southern hemispheres. Researchers have demonstrated highly significant correlations between the prevalence of MS and the degree of geographic latitude, the prevalence of the disease approaching zero in the tropics and increasing as one moves north or south.

The European distribution of MS by degrees of latitude is detailed in Table 7 which is taken from Gonzalez-Scarano *et al* (1986). Thus the Shetlands and Orkneys in Scotland have a prevalence rate of 309 per thousand compared with 12 per thousand in Sardinia. The world distribution of MS is illustrated in Figure 11 which is taken from Kurtzke (1980), and codes areas as being high, medium or low frequency, these denoting prevalence rates of $\geq$ 30, 5–29 and 0–4 per 100,000 population respectively.

In continents such as America, Kurtzke *et al* (1979) have studied MS incidence in US ex-servicemen (veterans) on the basis of place of residence prior to entry into the armed forces compared with controls. The case/control ratios for white males in each US state are consistent with the expected north-south gradient that would be predicted from Limburg's hypothesis.

As Table 7 indicates similar north-south pattern of MS prevalence is observed in Europe. In the case of the UK, Scotland has a relatively high rate of MS mortality and prevalence, as was illustrated earlier by the data in Figures 6 and 9. Particular attention has been paid to high pre-

Figure 11 **World distribution of MS.**



World-wide distribution of multiple sclerosis as of 1980. High-frequency areas are indicated in black, medium-frequency areas with dots, and low-frequency areas with diagonal dashes. Open areas are regions without data. South American frequencies are tentative.

Source Kurtzke (1980).

Table 7 **The prevalence of multiple sclerosis at various latitudes of Europe.**

Country	*Region*	*Latitude (°N)*	*Rate per 100,000*	*Year of study*	*Reference*
Iceland		64	58	1974	Kurtzke, Gudmundsson and Bergmann (1982)
Finland		63	40	1971	Wikstrom and Palo (1975)
Scotland	Shetlands, Orkneys	60	309	1974/77	Poskanzer *et al* (1980)
	North-east	57	178	1980	Downie and Phadke (1984)
England	Northumberland	55	42	1958	Poskanzer, Schapira and Miller (1963)
Ireland		53	66	1971	Brady *et al* (1977)
Germany	Hamburg	54	57	1960	Behrend (1966)
Netherlands	Groningen	53	58	1959	Dassel (1960)
England	Cornwall	51	63	1958	Hargreaves (1969)
Switzerland		47	52	1957	Georgi *et al* (1960/61)
Italy	Varese	46	15	1971	Cazzullo *et al* (1973)
	Novara	45	20	1976	Caputo *et al* (1979)
France	Marseille	43	14	1960	Behrend *et al* (1963)
Spain	Cataluna	42	6	1968	Oliveras *et al* (1968)
Italy	Bari	41	13	1975	Amprino *et al* (1977)
	Sardinia	39	12	1964	Caruso, Uras and Coni (1968)

Source Gonzalez-Scarano *et al* (1986).

valence rates in North East Scotland – specifically in the Orkney and Shetland Islands. Poskanzer and colleagues (1980) in a series of articles have explored this clustering of MS in the Orkneys, over and above that which would be predicted by the simple latitude hypothesis.

Generally then, the UK data presented here are broadly consistent with the north-south gradient of the Limburg hypothesis and this would appear to be particularly marked for the relationship between Scotland and the remainder of the United Kingdom.

What other factors differ with latitude that might help to explain differential prevalence of MS? First and foremost it should be noted that the observation itself might be a statistical artefact. Standards of medical care, awareness of the disease and accuracy in diagnosis are all elements which also vary with geography in this way. As Leibowitz and Alter (1967) report, in the northern hemisphere (in Europe and America for example) there is a north-south gradient in standards of care as measured by such things as infant mortality rates. Such differential standards might therefore permeate to awareness, diagnosis and treatment of MS. However the strong evidence from surveys such as Kurtzke's (1979) US veterans data would suggest that there remains a sharp north-south gradient in prevalence independent from geographical diagnostic bias.

Given the geographical distribution of MS, one way of learning more about the nature of the disease is to observe migrants from a low risk area to a high risk area and *vice versa*. Such information would allow the investigation of whether the disease was genetically determined (migration having little impact on individual risk) or whether it was environmentally determined – ie, by adopting the habits, diet and lifestyle of a low risk country does the migrant from a high risk area reduce his chances of developing MS?

A study by Dean *et al* (1976) of immigrants into Greater London found evidence that rates of MS were much lower among West Indians and natives of the Indian subcontinent, and this is taken as evidence that emigration from low risk areas to the United Kingdom (high risk) does not increase their risk. In contrast however, Kurtzke *et al* (1979b), examining north-south migration among US veterans have found that movement from high to low risk areas is associated with a decline in the migrant's chances of developing MS.

It is difficult to draw firm conclusions from the limited available evidence on migration. In terms of the nature of the causative agent behind MS, Acheson (1985) suggests that the epidemiological evidence points to '. . . an environmental influence (environment is used in its broadest sense here, and includes nutrition), the prevalence of which increases with distance from the equator (or protective influence with a reciprocal distribution), and which is operative in childhood and adolescence'.

Epidemiology III: Clues to a cause?

Having presented the available data on MS mortality and morbidity, there are two issues which must be addressed. The first is whether these data are consistent with the findings in the research literature. The second is whether these two areas combined can give some further clues as to the cause of the disease.

Nearly all recent surveys have agreed that multiple sclerosis occurs more frequently in women than in men, and furthermore the age of onset of the disease is slightly earlier in life. Acheson (1977), for example, in a review of MS epidemiology based on surveys conducted world-wide, concluded that women were 40 per cent more at risk of MS than men. Other studies such as that by Kurtzke *et al* (1979), using data from MS prevalence amongst US veterans have demonstrated age-adjusted differences in incidence of the order of 80 per cent higher for females than males. In summary, then, the data presented here for England and Wales are consistent with previous findings on the marked sex ratio in the incidence, prevalence and mortality from MS.

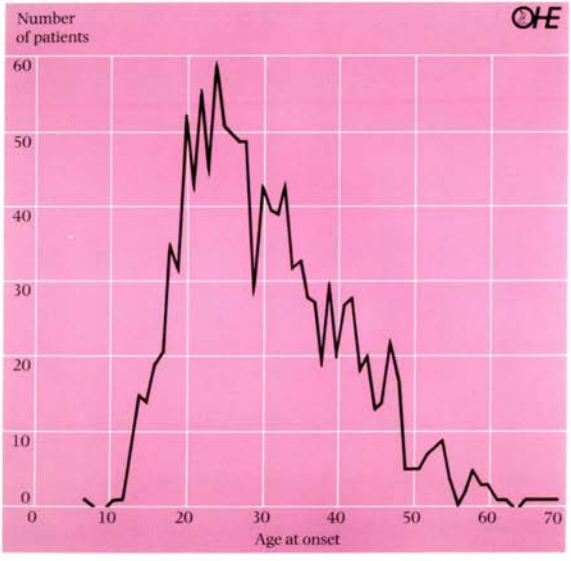
Incidence, prevalence and mortality from MS all have differing age profiles. A number of studies have examined the average age of onset of the disease and found this to be earlier for women than for men. Typically, onset of MS will be in the early 30s for the female and slightly later for the male. Matthews *et al* (1985, p49) concluded that '. . . there is general agreement that the mean age of onset is from 29–33, in most series being slightly earlier in women'. A recent Canadian study of 1,200 MS patients in London, Ontario by Ebers *et al* (1986) illustrates the typcal age of onset distribution and is reproduced here as Figure 12. In this study the average (mean) age of onset was found to be 30 years.

Concerning the age-specificity of prevalence rates, Acheson (1985, p8) notes that they '. . . behave in a substantially similar manner with age and sex, as do incidence rates, although the peak rates occur two to three decades later'. As he goes on to note, the age distribution of prevalence reaches its peak in the fifth decade of life, although female prevalence peaks sooner than male. Such an age distribution is consistent with the data presented here on consultation rates – a health care utilisation measure which will be weighted towards the age distribution of prevailing cases by virtue of their large numbers relative to new cases.

Typical age distributions for incidence (onset), prevalence and mortality have been drawn in Figure 13. (It should be stressed that the distributions are illustrative, not mapped from actual data.) The typical pattern therefore is for onset to be most likely to occur in 29–33 year olds. Secondly, prevailing cases in the community are most likely to fall into the 45–64 age bracket and finally, MS mortality is most frequent in the 65–74 year age group.

The geographical distribution of the disease is still one of its most puzzling aspects. One possible explanation may be some races are innately unsusceptible to MS. An example might be the Japanese who

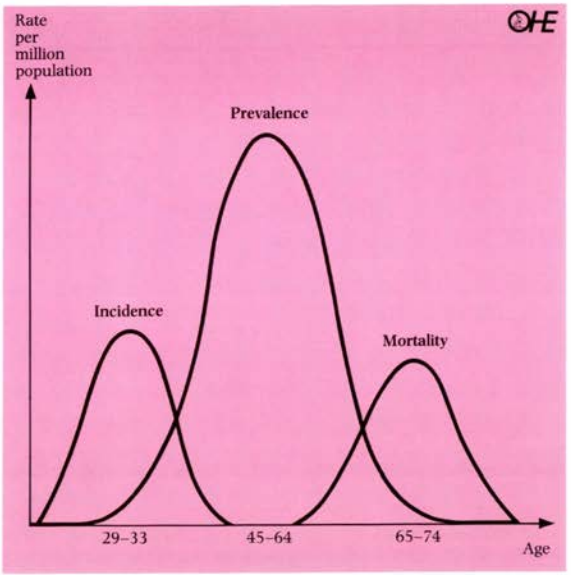
Figure 12 **Age of onset of multiple sclerosis in 1,200 patients in London, Ontario.**



Source Ebers *et al* (1986).

are a low risk group both in their home country and also generations later as immigrants living in the US (a high risk area) (Kurtzke *et al*, 1979). Furthermore, there has been little change in domestic Japanese rates in recent years despite the enormous changes in lifestyle and socio-economic climate (Kuroiwa *et al*, 1975). But the search for aetiological factors to 'explain' the distribution of the disease is one that must be undertaken with statistical caution. Association (the correlation of disease and some factor) is not proof of causation. As a cautionary aside Matthews (1978) makes this point by noting the close relationship between a map showing potato consumption and the distribution of MS although 'nobody seriously believes that eating potatoes causes MS'; but the idea is mentioned as an example of the difficulty in our state of ignorance of disproving the significance of a factor that fits rather well with a single observed fact about MS, in this case the geographical distribution.

Figure 13 **Typical age-specific disease pattern for multiple sclerosis.**



Note This diagram is intended as being illustrative of the distributions and is not drawn from specific data, hence the Y axis is not scaled. See text for details.

Roberts *et al* (1982) have argued that liability to developing MS is co-determined by both environmental and genetic factors. Studies have examined how probable it is that MS is hereditary – so called 'heredita-bility' percentages being calculated. Surveys suggest that there is an increased risk of between 30 to 50 per cent in offspring from MS sufferers. But such data must be treated with caution because observed differences may not be evidence of a genetic link but of a common environmental factor that both parent and offspring have been exposed to. However, it is likely that an increased 'susceptibility' can be passed on from parent to offspring.

Finally, some aetiological clues may lie in the age-sex distribution of MS incidence and prevalence. The consistently higher finding of MS in

women may be related to hormonal factors. (Fischman (1982), for example, reports how age cycles correspond closely with puberty and menopause (in women).) The question of the aetiology of the disease is referred to again in the discussion of treatment theories and practice.

Management and treatment of MS

The effectiveness of treatments for multiple sclerosis has long been a subject which arouses prejudice and emotion; a topic which often produces a good deal of heat and little light. There is, as yet, no definitive cure for MS but there are a number of treatments which may offer some benefit to some patients. Such speculative phrasing arises primarily from the problems researchers face in scientifically determining whether a particular treatment has any beneficial effect on the short- or long-term progress of the disease.

Judging the evidence

The established means of measuring the effectiveness of a treatment is the Randomised Controlled Trial (RCT). The random allocation of patients into treatment or control (comparison) groups affords the researcher a large degree of statistical rigour with which to test the hypothesis that a treatment has a beneficial impact. Unfortunately, the uncertain nature of MS prognosis, with its pattern of relapse and remission, makes MS a difficult disease to evaluate, even within the RCT framework.

First of all, there is the problem of which patients to include in the trial. Ideally, the researcher has a relatively homogeneous disease population to randomise between treatment and non-treatment. Yet the problems of MS diagnosis discussed earlier create difficulties in trial design because researchers may not be comparing 'like with like' in terms of disease severity. The second related problem is that the non-treatment or treatment group may be allocated a disproportionate number of patients who will, during the course of the trial, experience spontaneous remission independent from the effect of any treatment. Given the uncertainty of prognosis for individuals it is difficult to know how best such a bias in group allocation could be overcome. However, to the extent that such (unknowing) bias does occur the effect of any treatment will be over- or under-estimated.

Even if these problems of trial construction could be overcome, there is then the question of how to measure benefits or effectiveness to patients. In acute illness or surgery the survival of treatment groups can be calculated such that relative life-expectancy is the outcome measure for comparison. However, with chronic diseases such as MS, treatment effectiveness is likely to be more in terms of improvements in patient *quality* of life than in quantity. At one level, this might be measured in short-term symptomatic relief with respect to relapse rate or severity. More generally however, the search is for a treatment which can alter the long-term course of the disease such that the prob-

Table 8 **Disability status scale in MS.**

(In brackets are listed usual equivalents for defects in the Functional Systems (FS) listed below.)

0	Normal neurological examination (all grade 0 in FS).
1	No disability and minimal signs such as Babinski sign or vibratory decrease (grade 1 in FS).
2	Minimal disability, for example, slight weakness or mild gait, sensory, visumotor disturbance (one or two FS grade 2).
3	Moderate disability though fully ambulatory (for example, monoparesis, moderate ataxia, or combinations of lesser dysfunctions). (One or two functional systems grade 3 or several grade 2.)
4	Relatively severe disability though fully ambulatory and able to be self-sufficient and up and about for some twelve hours a day (one FS grade 4 or several grade 3 or less).
5	Disability severe enough to preclude ability to work full day without special provisions. Maximal motor function: walking unaided no more than several blocks (one FS grade 5 or combination of lesser grades).
6	Assistance (canes, crutches or brades) required for walking (combinations with more than one system grade 3 or worse).
7	Restricted to wheelchair but able to wheel self and enter and leave wheelchair alone (combinations with more than one system, grade 4 or worse, very rarely pyramidal system, grade 5 alone).
8	Restricted to bed but with effective use of arms (combinations usually grade 4 or above in several FS).
9	Totally helpless bed patients (combinations usually grade 4 or above in most functional systems).
10	Death due to multiple sclerosis.

The DSS is defined over 8 functional systems. Each system has a grading from 0 (normal) to 5 (maximal impairment). The systems are:

1 Pyramidal
2 Cerebellar
3 Brainstem
4 Sensory
5 Bowel and bladder
6 Visual and optic
7 Mental or cerebral
8 Other/miscellaneous (yes/no response)

Source Kurtzke (1961; 1981)

lems of disability and distress associated with the disease are alleviated or minimised for MS patients for the rest of their lives.

There are a number of ways in which changes in quality of life can be quantified. [For reviews of general approaches see Culyer (1983) and Teeling Smith (1985).] Measures vary in generality, and many are disease-specific. In the context of neurological diseases, and MS in particular, the Disability Status Scale (DSS) developed by Kurtzke (in its original and extended form) (1961; 1981) has become a widely used outcome measure for use in treatment evaluation.

The DSS is reproduced here in Table 8. As the name suggests the measure is focused on disability arising from neurological damage in eight 'functional systems' (eg. pyramidal, cerebellar, brainstem). The scale ranges from 0 (normal neurological examination) through increasing levels of disability to 10 (death due to MS). The scale is ordinal and can be applied to categorise MS patients as a means of charting disease progress or comparing treatment modalities in terms of impact on disability.

Kurtzke (1981) has also developed the Incapacity Scale for use with MS patients and this is reproduced here as Table 9. This measure is more readily interpretable in terms of the impact of the disease on an individual's quality of life because it examines a number of activities of daily living which the individual may have problems with. Areas such as bathing, dressing, ambulation, bladder function, societal role are all graded on a five-point scale. Again, the scale is categorical and there are no weights attached to the different areas of incapacity that may arise. Taken together the DSS and the Incapacity Scale can provide a broad categorisation of MS patients in terms of the impact of the disease on function status and disability.

Yet to determine relative health outcomes from MS treatment modalities it may not be sufficient simply to rate patients in terms of disability or function. The growing literature on health status (or quality of life) measurement stresses the multi-dimensional nature of health and the importance of measures which capture the patients' own perception of their health state or quality of life following some treatment. Robinson (1987), for example, in a review of clinical trials in MS has argued for the inclusion of more subjective indicators of quality of life such as the Nottingham Health Profile (Hunt *et al*, 1986). Not to use such subjective measures in treatment evaluation is to run the risk that significant differences between treatments in terms of impact on patient quality of life may be overlooked.

In the remainder of this section some of the main treatment modalities are reviewed. Yet the label of 'treatment' may be to overstate the case somewhat. More precisely the medical *management* of the disease is largely concerned with symptomatic relief and attempts to use new and existing medicines in order to retard the progress of the disease in the individual patient. Treatment, therefore, is used in the broadest sense of the word because none of the items discussed here can be said to be a 'cure' for the disease, although research for such a breakthrough continues.

Table 9 **The incapacity scale.**

1 **Stair climbing.** Ability to ascend and descend a flight of stairs of about 12 steps.
Grade 0 = normal.
Grade 1 = some difficulty but performed without aid.
Grade 2 = need for canes, braces, prostheses, or *dependent* upon banister to perform.
Grade 3 = need human assistance to perform.
Grade 4 = unable to perform; includes mechanical lifts.

2 **Ambulation.** Ability to walk on level ground or indoors some 50 m without rest.
Grade 0 = normal.
Grade 1 = some difficulty but performed without aid.
Grade 2 = need for canes, braces, prostheses to perform.
Grade 3 = need for human assistance or use of manual wheelchair which patient enters, leaves and maneuvers without aid.
Grade 4 = unable to perform; includes perambulation in a wheelchair and motorized wheelchair.

3 **Chair/bed transfer.** Ability to enter and leave regular chair and/or bed; includes wheelchair transfer as indicated.
Grade 0 = normal.
Grade 1 = some difficulty but performed without aid.
Grade 2 = need for adaptive or assistive devices such as trapeze, sling, bars, lift, sliding board to perform.
Grade 3 = requires human aid to perform.
Grade 4 = must be lifted/moved almost completely by another person.

4 **Toilet transfer.** Ability to seat self and arise from fixed toilet, and maintain position thereon.
Grade 0 = normal.
Grade 1 = some difficulty but performed without aid.
Grade 2 = need for adaptive or assistive devices such as bars, trapeze to accomplish.
Grade 3 = requires human aid to accomplish transfer or positioning.
Grade 4 = must be lifted/moved/held almost completely by another person.

5 **Bowel function.**
Grade 0 = normal.
Grade 1 = bowel retention not requiring more than occasional enemas or suppositories, self-administered.
Grade 2 = bowel retention requiring regular enemas or suppositories, self-administered, in order to induce evacuation; cleanses self.
Grade 3 = bowel retention requiring enemas or suppositories administered by another; needs assistance in cleansing; occasional incontinence; presence of colostomy tended by self.
Grade 4 = frequent soiling due either to incontinence or a poorly-maintained ostomy device, or an ostomy which patient cannot maintain without assistance.

6 **Bladder function.**
Grade 0 = normal.
Grade 1 = occasional hesitancy/urgency.
Grade 2 = frequent hesitancy/urgency/retention. Use of indwelling or external catheter applied and maintained by self.
Grade 3 = occasional incontinence; use of indwelling or external catheter applied and maintained by others; ileostomy or suprapubic cystostomy maintained by self.
Grade 4 = frequent incontinence; ostomy device which patient cannot maintain without assistance.

7 **Bathing.**
Grade 0 = normal.
Grade 1 = some difficulty with washing and drying self though performed without aid whether in tub or shower or by sponge-bathing, which ever is usual for the patient.
Grade 2 = need for assistive devices (trapezes, slings, lifts, shower or tub bars) in order to bathe self; need to bathe self outside tub/shower if that is his usual method.
Grade 3 = need for human assistance in bathing parts of body or in entry/exit/positioning in tub or shower.
Grade 4 = bathing performed by others (aside from face and hands).

8 **Dressing.**
Grade 0 = normal.
Grade 1 = some difficulty clothing self completely in standard garments, but accomplished by self.
Grade 2 = specially adapted clothing (special closures, elastic-laced shoes, front-closing garments) or devices (long shoe-horns, zipper extenders) required to dress self.
Grade 3 = need for human aid to accomplish; performs considerable portion him/herself.
Grade 4 = need for almost complete assistance; unable to dress self.

9 **Grooming.** Care of teeth/dentures and hair; shaving or application of cosmetics.
Grade 0 = normal.
Grade 1 = some difficulty but all tasks performed without aid.
Grade 2 = need for adaptive devices (electric razors or toothbrushes, special combs or brushes, arm rests or slings) but performed without aid.
Grade 3 = need for human aid to perform some of the tasks.
Grade 4 = almost all tasks performed by another person.

10 **Feeding.** Ingestion, mastication, swallowing of solids and liquids, and manipulation of the appropriate utensils.
Grade 0 = normal.
Grade 1 = some difficulty but performed without aid.
Grade 2 = need for adaptive devices (special feeding utensils, straws) or special preparation (portions pre-cut or minced, bread buttered) to feed self.

Grade 3 = need for human aid in delivery of food; dysphagia preventing solid diet; esophagostomy or gastrostomy maintained and utilized by self; tube-feeding performed by self.
Grade 4 = unable to feed self or to manage ostomies.

11 **Vision.**
Grade 0 = normal.
Grade 1 = lenses required or mild corrected visual acuity deficit (better than about 20/50 both eyes); able to read standard newspaper print.
Grade 2 = corrected acuity about 20/50 (6/15) or worse in the better eye; magnifying lenses or large print necessary for reading; one eye grade 4 and the other grade 0 or 1.
Grade 3 = corrected acuity about 20/100 (6/30) or worse in the better eye; essentially unable to read; one eye grade 4 and the other grade 2.
Grade 4 = legal blindness; corrected acuity 20/200 or worse in both eyes.

12 **Speech and hearing.** Verbal output and input for interpersonal communication purposes.
Grade 0 = normal; no subjective hearing loss; articulation and language appropriate to the culture.
Grade 1 = impaired hearing or articulation, not interfering with communication.
Grade 2 = deafness sufficient to require hearing aid and/or dysarthria interfering with communication.
Grade 3 = severe deafness compensated for by sign language or lip reading facility and/or severe dysarthria compensated for by sign language or self-written communication.
Grade 4 = severe deafness and/or dysarthria without effective compensation.

13 **Physical problems.** Presence of general medical and/or neurologic and/or orthopedic disorders. This would include MS
Grade 0 = no significant disorder present.
Grade 1 = disorder(s) not requiring active care; may be on maintenance medication; monitoring not required more often than every three months.
Grade 2 = disorder(s) requiring occasional monitoring by physician or nurse, more often than every three months but less often than weekly.
Grade 3 = disorder(s) requiring regular attention (at least weekly) by physician or nurse.
Grade 4 = disorder(s) requiring essentially daily attention by physician or nurse; usually in hospital.

14 **Societal role.** Primarily refers to patient's ordinary occupation, including housewife or student as applicable, as it may be modified by his impairment or disability.
Grade 0 = no impairment.
Grade 1 = performs usual role and tasks despite some difficulty with their performance.
Grade 2 = impairments require modification of usual role and tasks in nature, frequency or duration.

Grade 3 = impairments preclude usual role and tasks; unemployable outside sheltered workshop or very unique skills; generally dependent on assistance (public or private or family) to maintain situation in usual household.
Grade 4 = requires long-term institutional care or its equivalent if maintained at home by intensive nursing, whether societal or family.

15 **Fatigability.** This is a sense of overwhelming weakness or lassitude which dramatically alters baseline motor and co-ordination (occasionally visual or sensory) functions. It may be transient or persistent for hours or even days, and occurs at varying frequency; a very common complaint in MS.
Grade 0 = no fatigability.
Grade 1 = fatigability present but does not notably interfere with baseline physical function.
Grade 2 = fatigability causing intermittent and generally transient impairment of baseline physical function.
Grade 3 = fatigability causing intermittent transient loss or frequent moderate impairment of baseline physical function.
Grade 4 = fatigability which generally prevents prolonged or sustained physical function.

16 **Psychic (mood and mentation) function.**
Grade 0 = normal.
Grade 1 = mild mood or behaviour disturbance not interfering with usual function.
Grade 2 = moderate mood or behavior disturbance (eg, depression, anxiety) and/or mild mentation impairment with some interference with usual function.
Grade 3 = severe mood or behaviour disturbance (depression, euphoria, anxiety) and/or moderate mentation impairment and/or mild active psychotic reaction.
Grade 4 = severe mentation impairment or psychosis. (Note 'mentation impairment' includes mental retardation as well as 'organic brain syndrome' or 'dementia'.)

Source Kurtzke (1981).

Adrenocorticotrophic hormone (ACTH) and steroids

ACTH is a hormone, naturally secreted by the pituitary gland, which stimulates the production of steroids such as cortisone by the adrenal gland. It is not known how ACTH works, but when injected during an acute relapse there is evidence that it can speed recovery from relapse. The likely reason for this short-term effectiveness is that ACTH reduces the swelling in the plaques on the myelin sheath thus reducing fluid pressure on the axons (nerve fibres) and reducing restriction in the conduction of nerve impulses. As Matthews (1980, p68) notes however, there is still no evidence that the *extent* of recovery from relapse is influenced by ACTH, only the speed of recovery. Furthermore, there is

no evidence that ACTH will influence the long-term course of the disease.

In practice ACTH is used in short sharp bursts in response to acute relapse; a typical course of treatment being twice daily injections for two to four weeks following onset of relapse. There is little evidence that ACTH is an effective long-term therapy and the additional factor is that it is associated with the typical side-effects of steroid therapy such as water retention, loss of potassium, 'rounding' of the face (so-called 'moonface') and skin problems.

There is continued debate about the value of other oral steroids such as prednisone and prednisolone, particularly as a long-term therapy. Trials are currently being undertaken in the UK of high-dose methyl prednisolone in treatment of relapse; initially taken intravenously every few hours then tapered to orally over a period of weeks. Early studies of this method (Dowling *et al*, 1980) have produced promising results.

Immunosuppression

The evidence concerning the formation of the lesions on the myelin sheath suggests that they are caused either by an autoimmune response or that the immune system fails to protect the myelin against some external agent. As was discussed earlier, it is known that during periods of relapse the concentration of antibody cells (lymphocytes) increases. The simple logic of immunosuppressive therapy, as the name suggests, is to introduce some agent that will suppress the activity of the immune system in the body and hopefully reduce the damage being caused to the myelin by (possibly) the lymphocytes.

The common application of immunosuppression is in transplant surgery where, in order to stop the recipient's body 'rejecting' the alien donor tissue, an agent such as cyclosporin is given as a therapy which reduces the body's immunity so that it will not 'attack' the new organ. The immunological theory therefore, is that a course of a similar compound for MS patients might reduce the antibodies which are presumed (in this theory) to be causing the damage.

The evidence from controlled trials that immunosuppression with agents such as azathioprine has any beneficial impact is mixed. See for example Aimard *et al* (1978); Rosen (1979). The decision to treat with immunosuppression is a particularly difficult equation to balance because of the known long-term complications such as lymphoma (cancer of the lymph nodes). Therefore, the evidence of effectiveness would have to be particularly strong to outweigh the long-term risks of side-effects. When discussing this treatment modality it is appropriate to stress long-term risks because the course of treatment, to have maximum effect, would have to be life long – essentially a maintenance therapy which continues to hold the individual's antibodies at bay. There are trials of azathioprine currently being undertaken in the United Kingdom and the evidence on effectiveness from these will be carefully examined and set against the costs of such therapy in the short- and long-term.

Diet

As discussed earlier, the vast majority of theories concerning diet as an aetiological and treatment factor in MS have focused on the role of the many types of fat intake. The primary motivation behind such a theory was epidemiological rather than clinical. Swank (1950) noted the fall in multiple sclerosis incidence in Norway following the German occupation of the Second World War and argued that this fall was due to dietary change, particularly reductions in fat intake. Further contrasting incidence between inland and coastal areas, animal fats versus fish oils in diet, the hypothesis began to develop into a search for which types of fats or fatty acids were relevant, or which mechanisms for metabolising such fats were faulty.

As was mentioned earlier, a current theory is that there may be a fault with the way MS sufferers metabolise essential fatty acids: observed low levels of linoleic acid promoted treatments to supplement this deficiency. Although a number of trials of linoleic acid have been undertaken the evidence of effectiveness is mixed, due in no small part to the problems of MS treatments trial discussed earlier. Millar *et al* (1972) for example, suggested slight improvements in relapse rates and reductions in Kurtzke disability scores for patients given sunflower seed oil (high in linoleic acid) as a dietary supplement but differences were statistically non-significant.

A number of further trials and research have been undertaken by Bates and colleagues in Newcastle. In one double-blind randomised trial (in non-remitting disease) of polyunsaturated fatty acids, four treatment groups were compared in terms of the number and frequency of relapses following treatment. After two years of treatment there was found to be no difference in outcome between the various supplement regimes (Bates *et al*, 1977). Similarly, the same group examined the same regimes with patients who had acute remitting disease. There was found to be no difference in relapse rate between the treated and control groups although there was a small reduction in the severity and duration of relapses on the linoleic supplement.

The evidence that diet, in the form of controlling or supplementing the intake of polyunsaturated fatty acids (PUFAs), has any impact on MS is inconclusive, and research in this area continues. Both the MS Society and ARMS continue to fund research into the relationship between diet and MS. Trials to date have found some small indication that severity and duration of relapse may be reduced, however the overall history of the disease appears to remain unchanged with no beneficial impact on the frequency of relapse or the speed of deterioration. As Matthews (1985, p254) points out however, as long as controlling diet has no *harmful* effect then patients may benefit from such regimes insofar as they feel they are doing something *themselves* about the disease. This is an important theme to emphasise in the treatment of MS, where patients derive positive benefit from self-help, even if the evidence on beneficial clinical outcome is slim. To this end, Matthews argues that dietary substitution away from animal fats and towards vegetable oils might be encouraged.

Hyperbaric oxygen

An area of recent innovation in MS treatment which has caused a good deal of controversy is hyperbaric oxygen (HBO). The idea that HBO could be used to treat MS came from observing the illness in deep-sea divers who surfaced too quickly. This decompression sickness, known as 'the bends' can cause damage to the CNS apparently similar to that caused by MS. HBO had been used routinely since the 1930s to treat divers for this illness. An interesting innovation was to attempt to use HBO in the treatment of neurological disorders such as MS.

HBO is applied in either a large multi-patient pressure chamber or in a smaller chamber designed for one person. In the multi-patient chamber, the door is sealed and the chamber pressure raised by introducing high-pressure air. During the exposure, the patient periodically breathes 100 per cent oxygen from a face mask. The treatment period for oxygen inhalation is usually from 20 minutes to a maximum of an hour. In the single patient chamber the patient is placed in the chamber and the pressure is raised by introducing high-pressure oxygen. Thus, the patient not only breathes pure oxygen but is also surrounded by 100 per cent oxygen. The pressure setting that is used varies but is usually at least two atmospheres absolute (1520 mmHg).

Despite enthusiasm for HBO as a treatment, particularly from patient self-help groups such as Action for Research into Multiple Sclerosis (ARMS), the vast majority of evidence from trials of HBO suggests that it has no beneficial impact on the disease. Both the MS Society and ARMS have conducted trials with HBO. A recent and comprehensive double blind trial of HBO on 84 patients is reported by Wiles and colleagues (1986). They compare HBO (2 atmospheres with oxygen) with placebo (1.1 atmospheres, no oxygen) in chambers where face masks are not used but the atmosphere is 'ready mixed'. Patients were assessed before, immediately after and one month after treatment. The authors report that 'there was no clinically important or significant benefit in any of the four major criteria of outcome, namely, the patients' subjective opinion, the examiner's opinion, the score on the Kurtzke disability status scale, or the time taken to walk 30 metres'. Such results were the same as the earlier study on 60 patients in Newcastle (Barnes *et al.* 1985) commissioned by the MS Society.

Despite the paucity of evidence from clinical trials that HBO has any clinical efficacy, many MS sufferers are still keen to try and/or maintain such therapy. Enthusiasm is sparked or spurred-on by hearing of or knowing 'somebody' who did benefit from HBO. Although enthusiasm outstrips formal RCT evidence there is again the question of patients benefiting from doing *something* about their disease; but this is a benefit which is not immediately clinically discernible. To some extent the simple bringing together of patients into a group necessary for HBO will aid communication and lift spirits. In summary, however, the formal evidence is that HBO can do little if anything to cure or ameliorate MS.

Fringe theories

Given that the medical profession has so far been thwarted in its efforts

to find a cure for MS, there has been no shortage of 'alternative' or fringe treatment theories clamouring for recognition. When doctors can offer little by way of treatment, it is perhaps not surprising that many MS sufferers are prepared to put their faith in new ideas which, although they may not carry the full scientific stamp of approval, may offer some hope. One such fringe theory is that the venom from certain poisonous snakes may be beneficial to people with MS.

In 1955, Bill Haast was bitten by a highly poisonous snake – the Banded Krate from India. He did not die because he had been bitten by Cobras so many times before that he had effectively immunized himself against the venom. However, he did undergo hospitalisation and experienced symptoms similar to those of MS. The reasoning then followed that if such venom attacked the nervous system in this way, it might be possible to produce some form of vaccine-like compound from the venom that might be used in the treatment of MS.

At Bill Haast's Serpentarium in the USA, MS patients volunteer themselves to undergo a course of injections with a product called Proven which is made from venom that Haast 'milks' daily from his snakes. The venom comes from the Cobra, Krate and Viper. The raw materials for this product are also imported into the United Kingdom by a company in Middlesex who manufacture and distribute a similar product called Triven.

Many of Haast's patients claim that the venom treatment has brought benefit to them, and a number of patients are using Triven in the UK. The evidence however, is largely anecdotal. No controlled clinical trials of venom have been undertaken, in part because the medical profession do not accept the idea of venom as a treatment. Again, development of such fringe ideas has been undertaken by self-help groups outside the mainstream of the medical establishment.

Resource costs of multiple sclerosis

The existence of a disease such as multiple sclerosis imposes a burden on society in terms of the bed-days, GP consultations and other scarce health care resources consumed that will no longer be available for alternative uses. Black and Pole (1985) detailed how consumption of a number of such resources varies between disease groups. They therefore build up a 'burden of illness' picture and argue that such considerations are important in determining priorities for biomedical research.

The logical extension to enumeration of resource units consumed is to attempt to place a money value on them and hence move towards an estimate of the social cost of MS. The guiding principle behind the economist's definition of cost is very simple. A resource cost can be said to have been incurred as a result of a disease for either of two basic reasons: (i) resources are diverted from alternative uses, or (ii) output (production) is lost or reduced as a result of the disease. In the treatment of MS patients, for example, scarce health care resources will be

consumed – doctors, nurses, medicines etc – and these all have an alternative use and hence value; they could be used to treat patients in other disease groups. The notion of cost therefore is that of *opportunity cost*: by treating patient X you forgo the benefits that you would otherwise reap from using those same resources to treat patient Y.

The second strand to the costing approach is forgone or lost production due to illness. That is to say that the value forgone to society as a result of an individual's sickness absence from work is to be included in the calculus of the overall cost of the disease.

Costs can be categorised into direct and indirect costs. Typically this distinction is based on whether or not expenditure is incurred; hence hospitalisation is a source of expenditure (direct cost) while earnings figure is an opportunity cost of the disease and an indirect cost component. A broad outline of this distinction is as follows:

(i) **Direct Costs**
Treatment costs incurred by the health service, (eg),
– Hospital inpatient care
– Hospital outpatient care
– GP consultations
– GP prescriptions
– Community care facilities

(ii) **Indirect costs**
Production (output) lost due to:
– premature mortality (working years lost)
– morbidity episodes (working days lost)

The list of costs is by no means exhaustive. A significant limiting factor is the availability of published data with which to estimate the resource impact of a disease. A typical consequence of this shortage is that the *private* costs of the disease (ie, those that the individual and his/her family incurs) are typically under-represented in disease costings. Private costs can be direct (eg, expenditure as a result of disability such as house modifications) but typically they will be indirect with such items as forgone earnings by family and spouse who become full-time carers.

The absence of reliable private cost data is cause for particular concern with chronic diseases such as MS where the incidence of resource usage is likely to be weighted quite heavily away from the formal health care sector. This paucity of data on the private costs (family, spouse etc) of disability resulting from MS will give rise to an underestimate of the overall resource consequences of the disease, since the burden of care is likely to be distributed towards the informal – family and community – and away from the more formal public sector care provision.

Health service costs

In a parliamentary question in the House of Commons in 1984 the question of the health service cost of MS was raised:

> '*Mr Carter Jones* asked the Secretary of State for Social Services if he will assess the total costs incurred by the Government as a consequence of the incidence of multiple sclerosis.
>
> '*Mr Newton* (replying): Statutory services for people with multiple sclerosis form part of overall health and social services provision, and it is not possible to identify expenditure devoted to particular categories of disabled.'
>
> (*Hansard*, No 1328, 5 December 1984, Cols 224–225.)

The answer was, strictly speaking, true. However, it is possible to construct reasonable estimates of such expenditure by combining published data on activitiy measures such as bed-days with published cost data – eg, cost per inpatient day by hospital type. Such estimates are crude but can be used to establish the broad relativities of resource cost for discussion.

Hospital inpatient cost data can be obtained from costing returns published by the DHSS (1986) and cost per inpatient day figures are available by type of hospital. However there are no published data which disaggregate inpatient stay for MS by type of hospital. The assumption used here is the same as that put forward by an earlier study (*Economist* Intelligence Unit, 1974) that 5 per cent of days occur in partly acute hospitals and the remainder in long stay hospitals.

The data in Table 2 indicate that the mean length of stay in hospital is markedly higher for females than males in all age groups. In the 45–64 age group, for example, the mean length of stay for males was 35 days and for females 82 days. It is not immediately clear why this difference exists. In part it may be due to clinical considerations and complications arising. Secondly, it may be due to differential family/spouse support in the home – making it less easy to discharge females as early as males. The median length of stay is also reported which is significantly lower than the mean. This indicates a skewed distribution in length of stay with a small number of cases who have lengthy in-patient stays 'inflating' the mean. Combining length of stay and cost per day data it is estimated that the hospital cost of MS is approximately £13 million per year.

Few routine data are available on outpatient visits by disease group. To establish a minimum figure, data have been taken from the third National Morbidity Survey (of GPs) on referrals from GP to outpatient departments for patients consulting within ICD Chapter 6 (specific referral rates for MS not being available). Using this estimate, in conjunction with average cost data on outpatient visits to a partly acute hospital it is possible to arrive at an estimate of £0.8 million for outpatient care for MS.

An average cost for a GP consultation was estimated using available data on total GP workload and GP remuneration, and provided an estimated total of £1.7 million for 1986/87. The total cost of medicines prescribed in general practice for MS is estimated at £2.3 million for England and Wales in the same year. These costs are estimated by

Table 10 **Estimated costs of MS for the National Health Service in England and Wales; 1986/87.**

	£ million
Hospital inpatients	13.4
Hospital outpatients	0.8
GP consultations	1.7
GP prescriptions	2.3
Total	18.2

multiplying up the items prescribed by the basic NHS list price and then adjusting for additional charges such as dispensing fees and overheads.

These direct health service cost estimates are presented in Table 10 and suggest that annual health service expenditure on MS (1986/87 prices) is in the region of £18 million. In addition to these direct NHS costs must be added the costs of caring for the physically handicapped in long stay institutions maintained by the social services, local authorities and other private homes. An accurate costing for such community care for MS is difficult to make because data are not available which disaggregate the physically handicapped by cause of disability, but it probably exceeded £7 million in 1986/87.

A recent report by the Audit Commission (1986) estimates that in England and Wales in 1984 there were 5,200 'younger physically handicapped' individuals in local authority staffed homes, 4,100 in private and voluntary homes and a further 600 in supplementary benefit supported homes. What proportion of these 9,900 are institutionalised due to MS is difficult to determine. The study by the *Economist* Intelligence Unit (1974) states that 20 per cent as a proportion 'does not seem unlikely'. On this crude basis the cost of such community care would be in the region of £7.2 million per annum.

For a detailed analysis of direct costs it is also appropriate to quantify the use of support services such as community nurses, home helps and other facilities. Such detailed costing of community care is difficult to undertake for a particular disease group without specific prospective data collection. The methodology for such costing of care has been explored by Wright *et al* (1981) and they note the marked relationship between the level of functional disability and the use of resources both public and private. As and when MS patients develop the progressive form of the disease with the attendent severe disability they are therefore likely to be high cost care patients both in terms of public and private resources.

Indirect costs

Premature mortality due to MS is one indicator of the 'burden' of the disease on society. The extent of this burden can be determined by

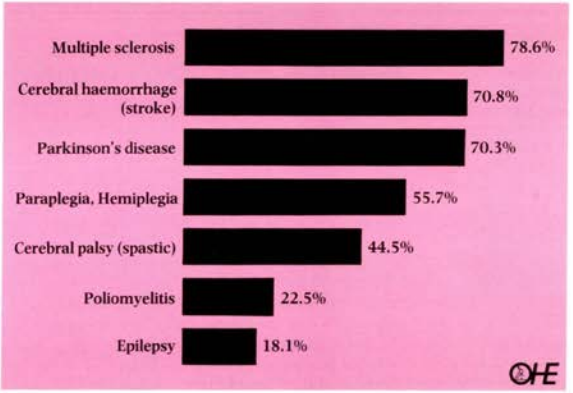
Table 11 **Life years annually lost due to multiple sclerosis (ICD 340), England and Wales 1985.**

(1) *Midpoint of 5 year age group*	*(2)* *Expected life years remaining [85–(1)]*	*(3)* *Deaths in 1984*	*Life years lost [(2)×(3)]*
17.5	67.5	1	67.5
22.5	62.5	5	312.5
27.5	57.5	12	690.0
32.5	52.5	31	1,627.5
37.5	47.5	35	1,662.5
42.5	42.5	50	2,125.0
47.5	37.5	78	2,925.0
52.5	32.5	102	3,315.0
57.5	27.5	113	3,107.5
62.5	22.5	143	3,217.5
		Sub total to 65 years	19,050.0
67.5	17.5	110	1,925.0
72.5	12.5	92	1,150.0
77.5	7.5	56	420.0
82.5	2.5	20	50.0
		Total to 85 years	22,595.0

relating MS deaths (by age group) to official estimates of 'normal' (average) life expectancy. This enables the calculation of future life-years lost due to multiple sclerosis. Future life years lost annually in England and Wales due to multiple sclerosis are presented in Table 11. A total of 19,050 future working years (to age 65) are lost each year due to MS. Including non-working years (to age 85) this figure increases to 22,595 years lost.

It is possible, and commonly practised, to place an estimated money value on future life years lost using the so-called human capital method. This method simply equates the future value of an individual to society with marketed (ie, wage earning) production of that individual. Such estimates, however, are often difficult to interpret (particularly in times of high unemployment) and also have the undesirable feature of attributing zero productive (marketable) value to survival beyond retirement from the labour force. No attempt has been made in this paper to include the *value* of future production foregone, although an estimate of future life-years lost is included.

Figure 14 **Proportion handicapped* by specific conditions.**



*Those individuals who are handicapped (appreciably) being in categories 1–6 of Harris' study. Thus of those surveyed, MS was the most handicapping of diseases.

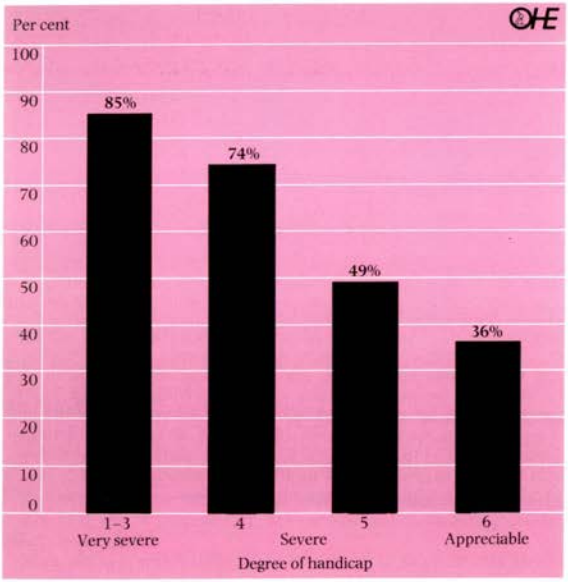
Source From Table AVI, Harris (1971).

The loss of *current* production is due to the fact that individuals with MS may be disabled to such an extent that they can no longer perform their job of work. The survey by Amelia Harris (1971) certainly indicated that MS was one of the most severely handicapping of diseases. Figure 14, taken from the Harris Survey, indicates that nearly 80 per cent of those surveyed who had MS were severely or appreciably handicapped compared with a disease such as Polio (22.5 per cent).

The survey also explored the relationship between degree of handicap and ability to work. This relationship is illustrated in Figure 15. Thus for individuals categorised as being 'severely handicapped' only 15 per cent were found to be still in employment. As a crude estimate of the impact of MS on working days lost, the percentages in Figure 15 have been applied to the original estimates (by disability category) by Harris of MS patients living at home, aged less than 65 with some appreciable (or greater) handicap. Thus an estimated 12,000 individuals are not working due to MS at a cost of some £100 million per annum in forgone earnings (production).

These estimates of resource consequences are summarised in Figure 16. It should be stressed however, that these form a minimum 'baseline' estimate to which must be added the (possibly substantial) indirect care and cost burden which falls on the individual spouse and family. The

Figure 15 **Proportions of the handicapped workforce* who are permanently disabled and unable to work again, by degree of handicap.**



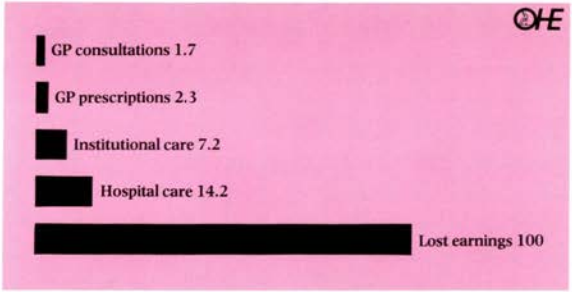
*Excludes retired and housewives.

Source Buckle (1971) (Part II of Harris Survey) Table 9.

available data do indicate that the majority of the physically handicapped (including MS) are cared for at home by a spouse or other relatives. Hence a more detailed costing should include the earnings forgone by such carers.

In summary, the limiting factor on an accurate costing of MS to society is the burden of care which is falling on the voluntary informal sector of the family and spouse. The costs estimated in this paper are approximate and are likely to be sensitive to different assumptions regarding the extent of disability in the community as a result of MS and furthermore the relationship between various disability levels and resource usage – both private and public.

Figure 16 **Annual costs of multiple sclerosis: England and Wales (1986/87 prices: £m).**



A final source of social cost which should be mentioned is the cost of research into MS. The Medical Research Council (MRC) does not provide a breakdown on spending by specific disease but in 1985/86 it spent £7.3 million on research into the central nervous system and £1.2 million on the neuromuscular system. In addition, the MS Society approved grants for research in MS of nearly £2 million in 1985 and self-help groups such as ARMS (Action for Research in Multiple Sclerosis) raised £339,000 in 1987 to finance research into the disease. There was also expenditure within the pharmaceutical industry which was relevant to neurological disorders such as MS.

Discussion: 'Prisoners of hope'

In 1978, a BBC Television *Horizon* programme on the subject of multiple sclerosis was simply called 'Prisoners of Hope'. Such a title captures the feelings of MS patients looking for a cure and hoping for a scientific breakthrough. In the last ten years, growth in MS research and the rapid progress in medical science has done much to maintain this spirit of hope, but still the cause and cure remain elusive.

If the history of medicine is any guide to the future it is quite possible that luck and judgement will lead to the discovery of an effective treatment which will then allow scientists to work backwards in order to determine the cause of MS. The most likely contender appears to be that MS is caused either directly by some viral infection of unknown origin or that indirectly such a virus provokes an autoimmune response within the cells of the body.

The idea of a viral infection directly attacking the nervous system invites comparison with poliomyelitis. In the case of this disease, scientists isolated the polio virus and used it to produce a prophylactic medicine – Salk vaccine. With MS the search continues to determine which, if any, of a number of viruses are the primary agent. But rather than a direct attack on the CNS it is more likely that the virus responsible forms an autoimmune response and it is this which does the damage to the nervous system. There are some obvious parallels to be drawn between this theory of MS and AIDS (Acquired Immune Deficiency Syndrome) which is the product of the Human Immunodeficiency Virus (HIV). An individual might be HIV positive but remain asymptomatic, healthy and not develop AIDS, similarly with MS this paper has documented how individuals may have some virus present, may have lesions visible in the CNS but still may not develop MS symptoms. Unlike HIV and AIDS however, MS cannot be transmitted from one person to another.

Other diseases which have proved mysteries in the past may also be the result of auto-immune responses. Another example is rheumatoid arthritis where scientists now believe a similar process to MS may be occurring where suddenly some (as yet unknown) 'trigger' causes the body's immune system to attack the joints in the body causing the erosion and subsequent pain and disability of arthritis.

If MS (and possibly rheumatoid arthritis) are the result of an AIDS-type virus then the millions of pounds currently being invested in AIDS research may provide some valuable 'spin-off' knowledge about the immune system in relation to such diseases. Alternatively, it may be that treatment advances in the use of immunosuppressants such as azathioprine may yield new knowledge concerning why and how the body's immune system is involved with MS.

Of the treatments that are available for MS, none can be said to be effective in the sense of changing the course of the disease. Some treatments, such as steroids like ACTH, are useful in the management of acute relapse but offer no long-term benefit. Dietary regulation, such as reducing fatty acid intake and supplementation with linoleic and other

essential fatty acids provides some limited evidence of slight reductions in the severity of relapse. Some of the biggest claims for benefit, such as preventing relapse, come from advocates of immunosuppression. Although the results of current trials are eagerly awaited, a life-long regime of azathioprine is a costly therapy not least of all in terms of the known long-term risks of malignant tumours.

Obviously prevention is preferred to cure. If a treatment were available it would be of little use after the nerve fibres had been severed and the central nervous system permanently damaged. What is needed is some form of prophylactic treatment, similar to the polio vaccine, which can be used to generate population immunity or used selectively on those at risk. But this raises the problem of how to identify those at risk or more generally how to diagnose MS early such that treatment might begin. Definitive diagnosis can still only be made *post mortem*, although the dawn of MRI and other techniques has increased the accuracy of *ante mortem* diagnosis. The main problem is that, unlike biopsies taken from cancerous tissue, the cells thought to be diseased are sealed in the CNS and cannot be sampled for laboratory investigation; the next best solution is to examine the cerebrospinal fluid that surrounds the CNS by lumbar puncture.

Research in the areas of treatment and diagnosis are obviously important priorities within the MS programme but so too is basic information from epidemiological studies. Two areas might be emphasised here. The first are studies (such as that soon to be published by OPCS) which give some detailed survey data on the prevalence of disability in the community attributable to diseases such as MS. It has been stressed in this paper that simple health care utilisation measures are poor proxies for chronic disease prevalence and more detailed information on the precise burden of illness would be valuable. The second area of epidemiological study which is of value is the following of cohorts of MS patients so that a more precise history of the disease might be documented allowing some reduction in the uncertainty of prognosis.

An important distinction throughout this paper has been that between impairment, disability and handicap. MS patients experience all three elements to a greater or lesser extent. Clinical judgement and medical technology can detect impairment in the body (eg, presence of lesions) which may be asymptomatic and remain so. For many people however, this impairment develops into the typical physical disabilities of MS. But the degree of *handicap* that an individual experiences is not a clinical or physiological assessment – it is determined by the society and environment in which we live. On this front, the attitude of society has made quantum leaps forward. The work conditions and social mobility of the disabled is undoubtedly improving and this reduces the degree of handicap that MS patients are experiencing, having a positive impact on their quality of life.

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To undertake research on the economic aspects of medical care.

To investigate other health and social problems.

To collect data from other countries.

To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support and discussions on research problems with any persons or bodies interested in its work.