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The relationship between relapse and disability in multiple sclerosis

The Relationship between Relapse and Disability in Multiple Sclerosis

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Abstract

Primary Aim: To describe the relationship between relapse and disability in multiple sclerosis.

Introduction: The relationship between relapse and disability in multiple sclerosis is presently unclear. Whilst natural history studies have confirmed the disabling effects of insidious disease progression they have suggested that relapse, the clinically defining feature of the majority of cases multiple sclerosis, is largely unrelated to disability. However the major therapeutic strategies currently in use against multiple sclerosis are known only to ameliorate relapses and their ability to prevent long term disability is not presently based on evidence but faith in a long presumed, but unproven relationship between relapse, disease progression and disability.

Method: A cross sectional study of 150 patients with multiple sclerosis was performed. Details of previous relapses and current impairment and disability were collected. Statistical analysis was performed to see if the character of preceding relapses correlated with the character of current disability.

Main Results and Conclusions: Relapses do cause relevant chronic impairment, however for a number of disease and scale related reasons this fails to translate into chronic disability. Disease related reasons include an apparent extra resistance of motor pathways to relapse, whilst scale related reasons include the widespread use of disability scales that are heavily predicated upon motor pathway dysfunction and less sensitive to sensory pathway dysfunction. We conclude that many of the paradox observed in multiple sclerosis tell us as much if not more about the tools used to observe the disease, as they do about the disease itself.

For Ingrid, Louis and Isla

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Author's declaration

I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original, except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other academic ward. Any views expressed in the dissertation are those of the author.

Signed:..... Date:9th December 2008.

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Chapter 1: Introduction

The aims of this thesis are as follows:

1. **To describe the relationship between relapse and disability in multiple sclerosis.**
2. **To describe the neurological deficits encountered during relapses of multiple sclerosis.**
3. **To describe in detail the neurological deficits at prevalence in a defined population of patients with multiple sclerosis.**

Multiple sclerosis is a disease of the central nervous system and frequently leads to chronic disability. Jean-Martin Charcot was the first to recognise the basic clinico-pathological spectrum of the disease in the latter half of the 19th century.

Multiple sclerosis may occur at any age although onset is most common in the 3rd and 4th decades of life. It is approximately twice as common in females as males. It is recognised to be rare in equatorial regions and become progressively commoner as one moves towards the poles. Prevalence figures of approximately 1 in 1000 in Western countries[1] are typical. There are several commonly recognised temporal disease patterns including[2] relapsing-remitting, secondary progressive and primary progressive disease sub-types.

Several aspects of multiple sclerosis remain enigmatic, these include:

- **Pathogenesis**. A combination of environmental and genetic factors is a correct but largely unhelpful solution. Exactly which environmental and genetic factors remain unknown.
- **Pathology**. Whilst the pathology of the later stages of the disease have been described in minute detail and heavily implicate inflammatory demyelination, descriptions of the earliest MS lesion are rare[3] and suggest that inflammation may be a partially adaptive response to an alternative primary pathology[4].
- **Clinical disease course**. The relationship between relapse, disease progression and long term disability remains unclear. We do know that the relapse free disease subtype (primary progressive disease) has the worst

prognosis[5] and that the course of secondary progressive disease is unaffected by antecedent relapses[6]. However it remains received, although unproven, wisdom that relapses shape future disability[7] and consequently that reducing relapses will have long-lasting prognostic benefits[8].

- **Treatment.** Despite considerable research and investment there have been no cures and no treatments that have conclusively altered the long-term natural history of multiple sclerosis[9].

Whilst the principal dilemma remains with the primary pathology of multiple sclerosis we believe useful inferences can be derived from a purely clinical study. Whether or not inflammation is the primary pathology[3], its clinical hallmark, the acute relapse, bears an uncertain relationship to the chronic disability. In order to understand the possible rationale for this it is necessary to look in further detail at the following areas of multiple sclerosis: basic terminology, natural history, pathology, radiology and therapy with a special emphasis on the relationship between relapse and disability.

(1) The basic terminology of multiple sclerosis

The natural history of multiple sclerosis is heterogeneous with regard to the individual and can range from a fatal index relapse paralysing respiration to a pair of mild sensory relapses with no permanent deficit. Although a comprehensive record of the natural history of multiple sclerosis has been difficult to achieve (for reasons which will be discussed later) there are basic clinical disease features and temporal sub-types that merit discussion.

There are two basic clinical phenomena that underlie multiple sclerosis: the relapse and disease progression. Relapses are thought to be the clinical expression of acute inflammatory focal lesions disseminated in the central nervous system, whereas progression is less well understood but is traditionally considered to reflect the occurrence of chronic demyelination, axonal loss, and gliosis. Indeed the relationship, or non-relationship, between these two entities[4;10-12] and the reasons behind this are critical to the paradigm shift in multiple sclerosis theory. Clinically relapse and progression both refer to deterioration in a patient with multiple sclerosis,

the distinction is in the timing. In broad terms a relapse occurs over days or weeks whilst progression occurs over months or years.

The **relapse** has been defined as an '*episode of neurological disturbance of the kind seen in MS, when clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature. Although there was some divergence of opinion, the group agreed that, for general diagnostic purposes, an attack, defined either by subjective report or by objective observation, should last for at least 24 hours*[13]*. This assumes that there is expert clinical assessment that the event is not a pseudoattack, such as might be caused by a change in core body temperature*[14] *or infection. Whereas suspicion of an attack may be provided by subjective historical reports from the patient, objective clinical findings of a lesion are required to make a diagnosis of MS. Single paroxysmal episodes (eg, a tonic spasm) do not constitute a relapse, but multiple episodes occurring over not less than 24 hours do.*'[15]

Disease **progression** refers to an insidious deterioration of neurological function over time. The period of time over which progression must occur is not dependent upon known pathological correlates but rather varies according to purpose. Generally for secondary progression, where the diagnosis of multiple sclerosis is already made, a period of six months is acceptable[10;16]. In progressive onset disease the differential diagnosis is wider and includes several treatable possibilities such as compressive disc disease and vitamin B12 deficiency. For this reason the McDonald criteria require a period of 12 months sustained disease progression (as well as positive oligoclonal bands) in order to make a diagnosis of primary progressive MS without the aid of MRI. Certainly a longer period of disease progression lessens the chances of confusing relapse and progression.

An attempt to achieve international consensus on the varying temporal phenotypes within multiple sclerosis has highlighted inconsistencies[2]. Researchers frequently use different terms for the same phenomenon and similar terms for different phenomena. Accepting that a democratic approach to defining the temporal course of multiple sclerosis is probably the best compromise we must also recognise that pathological processes are likely unaccountable to public opinion. The results of the survey

suggested the following disease sub-types[2]: Relapsing-remitting, primary progressive, secondary progressive, progressive relapsing, benign and malignant multiple sclerosis (see figure 1-1). The term relapsing-progressive multiple sclerosis was agreed to be a variant of secondary progressive disease and the distinction was deemed to be unhelpful.

(i) Relapsing-remitting multiple sclerosis

This comprises 'clearly defined relapses with full recovery or with sequellae and residual deficit upon recovery; periods between disease relapses characterised by a lack of disease progression'.

(ii) Primary progressive multiple sclerosis

This comprises 'disease progression from onset with occasional plateaus and temporary minor improvements allowed'. Approximately 10-15% of patients with multiple sclerosis have primary progressive disease[17].

(iii) Secondary progressive multiple sclerosis

This comprises an 'initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus'. With prolonged follow up approximately 10-15%[17] of relapsing remitting patients do not enter the secondary progressive phase.

(iv) Progressive-relapsing multiple sclerosis

This comprises 'progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression.

Benign and malignant are additional terms that can co-exist with any of the above disease sub-types:

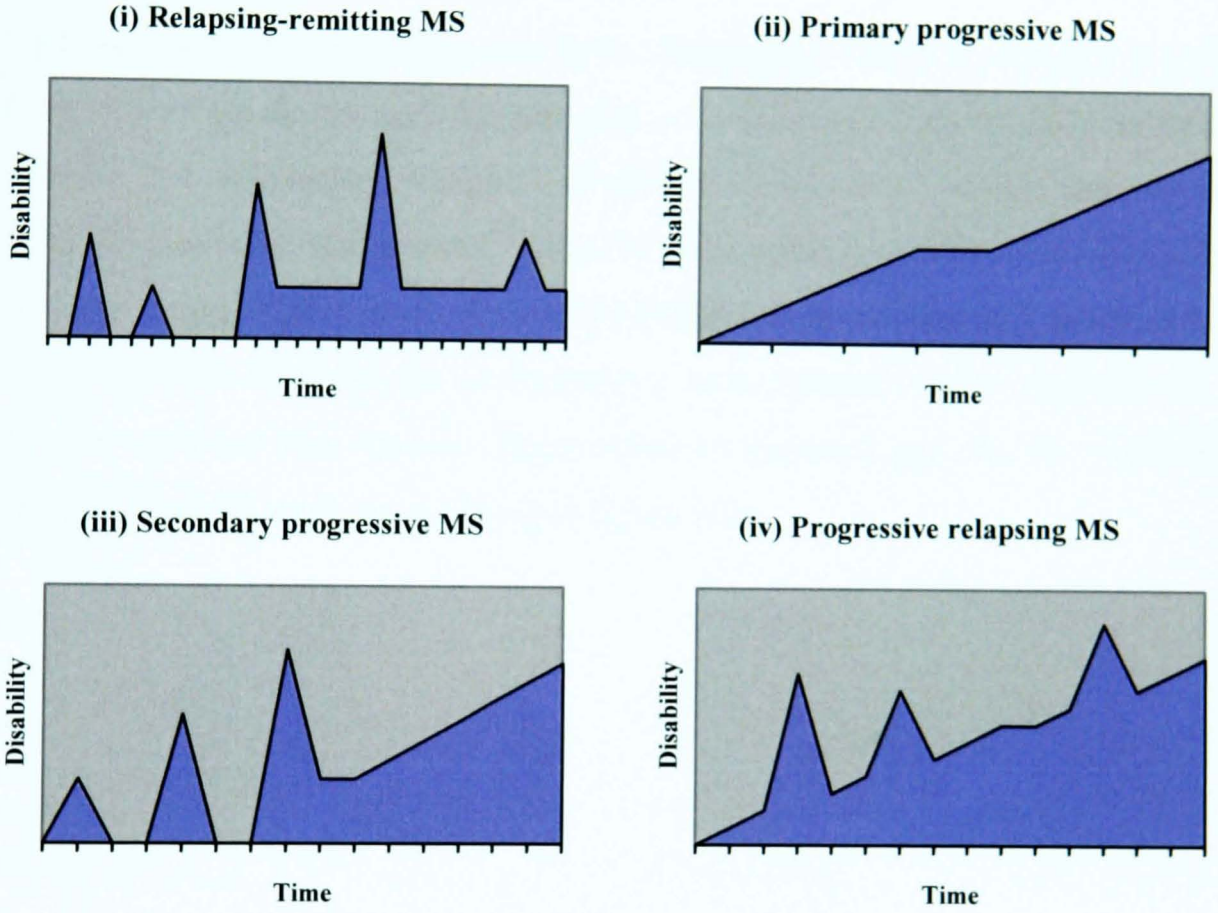
(v) Benign multiple sclerosis

This comprises 'disease in which the patient remains fully functional in all neurological systems 15 years after disease onset'.

(vi) Malignant multiple sclerosis

This comprises 'disease with a rapid progressive course leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset'.

Figure 1-1: The four sub-types of multiple sclerosis



(2) The natural history of multiple sclerosis

The ideal natural history study would include a population-based cohort being identified at the onset and then closely followed up for the duration of the disease. Several features of multiple sclerosis have made this challenging. Ascertainment is an obvious problem. Patients may simply not attend their local doctor, let alone be referred to a research interested referral unit. The continuing absence of a definitive, diagnostic test make it impossible to pick up all cases at their inception. Clinical and

para-clinical information increasingly allow for the creation of diagnostic criteria, of which the McDonald criteria[15] are the most recent, but fulfilling these criteria is subtly different from actually having the disease. Often multiple sclerosis can only be confidently diagnosed retrospectively which hinders prospective observation. Hospital based series have a natural bias towards more severe disease. The chronicity of the disease makes follow up over many years very difficult. Whilst we cannot be sure that existing treatments are effective at altering the long term natural history of multiple sclerosis the obverse is also true. Therefore the opportunity for recording the natural history of multiple sclerosis may, hopefully, have already passed.

Obtaining hard 'endpoints' has also been challenging. Multiple sclerosis is a disease principally of morbidity and not mortality so death is not a particularly enlightening endpoint. For this reason Kurtzke's disability status score[18] (DSS) and subsequent expanded disability status score[19] (EDSS) have proved popular. However although this scale ranges from zero to ten and the EDSS has introduced half points (a total of twenty different descriptions of disability), most natural history studies have used only four of these descriptions. These relate to impaired gait (4), the walking stick (6), wheelchair (7) and grave (10) (see figure 1-2).

Figure 1-2: Expanded disability status scores commonly used in natural history studies.

EDSS score	Description
4	Limited walking ability but able to walk for more than 500 metres without aid or rest.
6	Ability to walk with unilateral support no more than 100 m without rest.
7	Ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support.
10	Death due to multiple sclerosis.

The advantages of these points are that they are relatively simple and bear translation. Whilst newer scales[20;21] should undoubtedly be adopted for therapeutic trials in multiple sclerosis, the EDSS at present is the language of natural history in multiple sclerosis.

Of the numerous natural history studies of multiple sclerosis two merit individual consideration. These are the London, Ontario and the Lyon cohorts.

(i) The London, Ontario cohort

A study of the natural history of untreated multiple sclerosis has been carried out in London, Ontario, Canada, over the past generation[5;11;17;22-24] chiefly supervised by George Ebers. The MS clinic at the University Hospital in London, Canada, was established in 1972. This clinic has been able to study a geographically based population of patients longitudinally by means of regular follow up. Stringent effort has been made to follow up the benign and advanced disease courses, which are often lost to clinic based series due to apathy and institutionalisation respectively. The study also benefits from an internal control suggesting near complete ascertainment. A geographical subgroup of their patients from Middlesex county were the subject of a formal prevalence study[25] that showed 90% ascertainment of multiple sclerosis cases. There are now some 25,000 patient-years of follow-up in a cohort of 1099 individuals.

The data reveals that a number of factors are associated with long-term outcome of multiple sclerosis. The Ontario study shows several clinical variables that can be used to evaluate prognosis. The two most important indicators of a poor prognosis are the development of a progressive deficit and time to onset of progressive deficit. In addition, and independently, a high number of relapses in the first and second year is associated with a significantly shorter time to EDSS 6, as is the development of early unremitting disability.

The study also failed to find any available clinical features that distinguish primary progressive and secondary progressive multiple sclerosis (an assertion we seek to examine in Chapter 2) raising the question of whether these are fundamentally the same disease[24]. The clinical similarities between primary and secondary progressive disease would suggest that relapses, a preceding feature of secondary progressive but not primary progressive disease, do not determine chronic disability.

This leaves the problem of explaining the ultimately deleterious effect of a high number of relapses in the first and second year of the disease[22]. One possibility[11] is that relapses may be associated with, rather than the cause of disability in multiple sclerosis. By way of example as steroids are frequently used to treat relapses one might also expect to find a higher usage of steroids in association with a more severe disease course, but one could not reasonably propose that the steroids had caused the disability. If inflammation and their resultant relapses are an adaptive[26,27] (albeit frequently maladaptive) response to an as yet unidentified primary pathology[3,4,26,28] then, much as with steroids, we may expect to find an association between relapses and disability without causation.

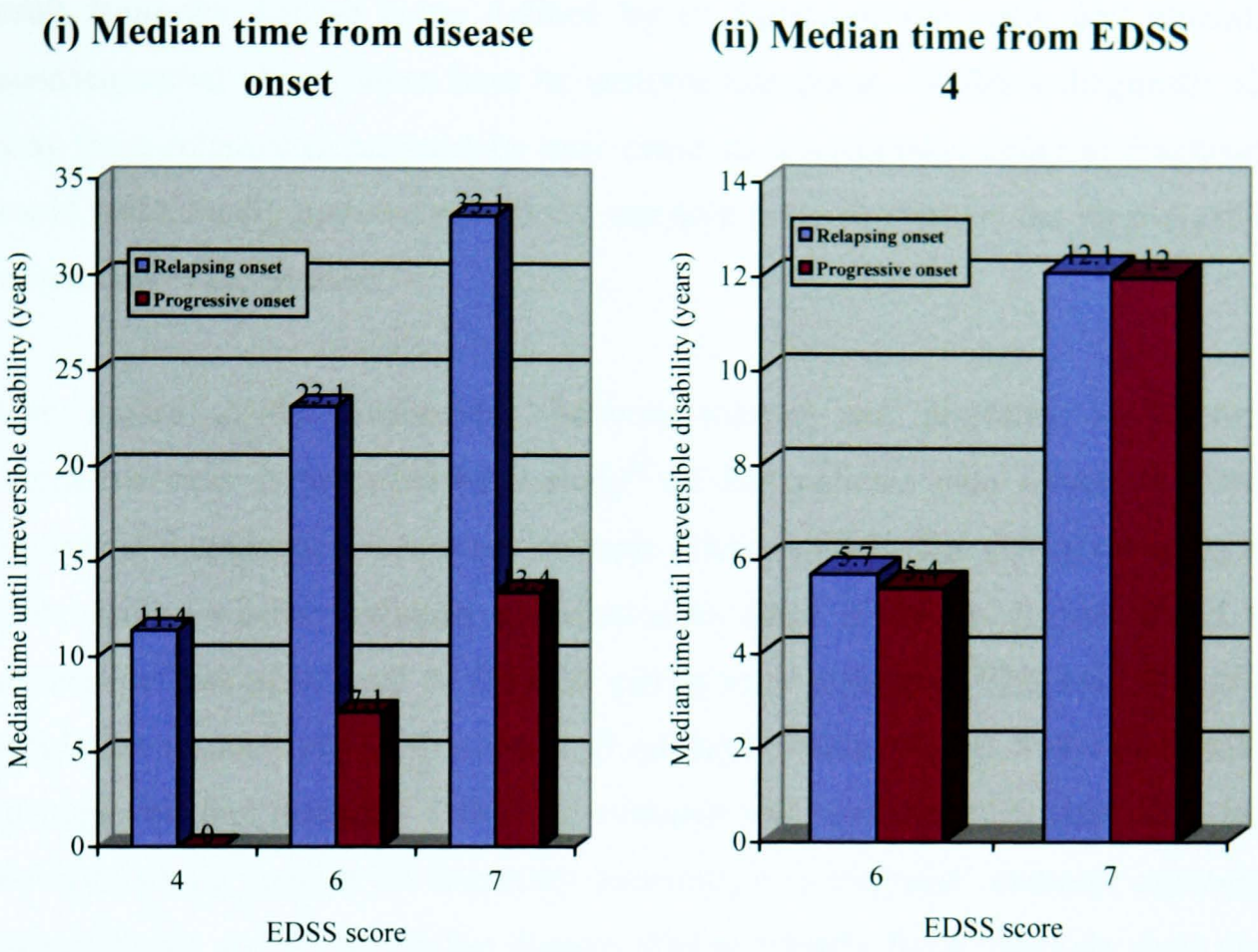
(ii) The Lyon, France cohort

The Clinique de Neurologie in Lyons, France, has been patiently recording the clinical details of multiple sclerosis patients since 1976 under the guidance of Christian Confavreux. The European Database for Multiple Sclerosis (EDMUS)[29] has been used to record the information since 1990. At the patient's initial visit retrospective details of the disease were recorded but subsequent assessment was annual and prospective. A total of 1844 patients with clinically definite or probable

multiple sclerosis as defined by the Poser criteria[13] were identified. The average disease duration was 11 years. 1562 of these patients had relapsing-remitting onset disease compared with 282 (15.3%) with primary progressive disease. The relationship between relapse onset (relapsing-remitting and secondary progressive) and progressive onset (primary progressive) disease with regard to irreversible disability was examined[10].

In the whole group the median time from disease onset to an EDSS of 4, 6 and 7 was 8.4, 20.1 and 29.9 years respectively. Subgroup analysis confirmed that primary progressive disease was associated with a much shorter time from onset to a score of EDSS 4. However this difference was lost once an EDSS score of 4 was obtained (see figure 1-3). This suggests that once walking becomes limited the pathological processes are unrelated to previous disease activity including relapses[6]. In addition super imposed relapses on either primary or secondary progressive disease were not found to hasten disability progression.

Figure 1-3: The relationship between time from disease onset (i) and time from EDSS 4 (ii) until fixed disability[10].



Further analysis by the Lyon group[6] found that many of the factors traditionally associated with a poor prognosis in multiple sclerosis were only relevant up until an EDSS score of 4 had been attained. Male sex, greater age at onset, incomplete recovery from the first relapse, shorter time to the second neurological episode, and an increasing number of relapses in the first 5 years of the disease were all associated with a significantly ($p<0.05$) shorter time from disease onset to an EDSS of 4. However none of the above factors had any significant ($p>0.05$) effect on time from EDSS 4 to EDSS 6.

The authors believe that this further indicates that multiple sclerosis is a two-stage disease comprising an initial phase of irregular duration influenced by clinical variables, and a second phase that is independent of baseline characteristics, course, signs or symptoms assessed at the onset of the disease. This suggests that early focal inflammation of the central nervous system and subsequent neurodegeneration are largely unrelated phenomena. In retrospect the poor prognosis in relapse free primary progressive disease had already eloquently made this point. Therefore the 'common pathway' of multiple sclerosis appears to exist at the later rather than the earliest

stages of the disease. Indeed some of the problems of multiple sclerosis research may result from the disease being defined by its heterogeneous early and ultimately inconsequential phase rather than its uniform late phase. Whilst a diagnostic shift away from relapses to progression may cause an unacceptable delay in diagnosis it would undoubtedly increase specificity and help focus therapy on the most disabling component of the disease.

With regard to the relationship between relapse and disability an important alternative view is provided by a study[30] of 224 patients who served as placebo controls in therapeutic randomised multiple sclerosis trials. The aim of the study was to determine whether relapses contributed to fixed disability. It was found that residual deficits of 0.5 and >1.0 EDSS points were present in 42% and 28% of the population respectively at an average of 64 days after a relapse. Subsequent follow up suggested that disability following a relapse was sustained over time. This study provides strong support for disability accruing in a 'stepwise' manner, consequent upon relapses, during the earlier disease phases. Clearly fixed disability does occur during the relapsing remitting disease phase in advance of classical secondary progression, but is it all from incomplete recovery from relapse? The only other conceivable way in which disability could be formed in the relapsing remitting phase is by concurrent early insidious disease progression. Ebers has suggested that all patients may begin progressing early in the course of the disease, but that this is extrememly difficult to measure i.e. EDSS 1[23]. If progression does occur in the relapsing remitting phase it is likely to be at a slower rate than in classical progressive disease[10]. Clinical experience combined with popular teaching[2] showing horizontal plateaus rather than gentle inclines between relapses has rendered any relapsing-remitting progressive disease clinically undetectable. There are 2 reasons not to completely discount the possibility.

Firstly, from experience with primary progressive disease we know that the earliest stages of progression are difficult for both patient and clinician to reliably detect and diagnose. The median time from onset of symptoms to diagnosis in the London, Ontario primary progressive cohort was initially 8 years[5]. The median EDSS at presentation in the Lyon cohort of primary progressive disease was 4[10]. One assumes that these patients had gradually ascended from EDSS 1 through to 4 over a

sufficient period of time so as to make the progression virtually invisible to patient and clinician. It is therefore possible that the earliest stages of relapsing-remitting disease are similarly affected by an undetected progressive phase.

Secondly, when using disability measures such as the EDSS, which is heavily predicated towards mobility, a gradual deterioration in non-motile neurological systems will probably not affect the EDSS score, giving the illusion of stable disease. Even without using scales such as the EDSS to monitor disease activity the clinician may be reluctant to diagnose the secondary progressive phase until it has become blatantly obvious. The reasons for this might include the associated poor prognosis[10] effect on patient morale and the need to withdraw drug therapies[31;32]. A parallel study[32] of relapsing-remitting patients who had not suffered a clear relapse over similar time periods might have helped to show whether progression in addition to relapses contributes to fixed disability during the relapsing remitting phase.

The studies and theories of Confavreux[6;10] and Lublin[30] are in fact not mutually exclusive. Together they indicate that in the classical relapsing-remitting disease disability can be accrued in a stepwise manner at a slower rate and then subsequently in a more rapid progressive manner. Lublin[30] has suggested that Confavreux's results may indicate that it is the later stages of the EDSS[19] and not multiple sclerosis that is insensitive to early relapses although this is unproven. Clinical scales such as the EDSS are one-dimensional. Relapses as part of natural history studies are often recorded as a binary event: 0 – no relapse or 1 – relapse. Whilst simplicity is a common component of successful research, it is reasonable to believe that accurate assessment of complex, multi-dimensional phenomena such as disability and relapses may require a qualitative, as well as a quantitative, approach.

A qualitative study of the nature of disability during relapses, and that in chronic progressive disease, is a powerful approach to answering the question of whether or not disability in multiple sclerosis is related to relapse. If relapse and chronic disability are related then one would expect them to be of a similar quality within an individual.

(3) The pathology of multiple sclerosis

The pathology of multiple sclerosis ***is*** the disease. For obvious ethical and practical reasons it is not possible to monitor the pathology of multiple sclerosis *in vivo*. Autopsy pathology is commonly available from end stage disease but even this is becoming a scarce commodity[33;34]. Opportunities to examine the earliest disease stages are as rare[3] as they are informative. For these and other reasons radiological techniques have become necessary to aid the study of disease activity *in vivo*.

The basic clinical features of multiple sclerosis probably have a distinct pathological basis. Relapses are considered to be the clinical expression of acute inflammatory central nervous system demyelination whilst remission is probably due to resolution of inflammation, sodium channel redistribution and remyelination. Progression is likely to reflect chronic demyelination, gliosis and axonal loss[35]. Although first noticed by Charcot over 100 years ago the importance of axonal loss[36;37] has recently been rediscovered.

The most obvious macroscopic feature of multiple sclerosis pathology is the demyelinating plaque whose plurality came to name the disease. Initial descriptions indicated that these were only to be found in white matter although it appears grey matter is also affected[38]. It does however remain the case that grey matter provides excellent camouflage for the grey demyelinating plaque. Away from the plaque all is probably not normal either. The normal appearing white and grey (NAWGM) is normal only in macroscopic appearance[39-41]. Whilst the histopathological damage is evidently less in the NAWGM than in plaque matter it should be remembered that even in the central nervous system with a high lesion load there will be much more NAWGM than plaque matter. Therefore a minor functional deficit of NAWGM may be more disabling than even a severe functional deficit in the plaque matter.

(i) The multiple sclerosis plaque

Demyelinating plaques may occur anywhere in the CNS. They are, however, more common in certain areas[7]. In the forebrain, the periventricular subependymal zone, the border between cortex and white sub cortex, the optic nerves and chiasm are preferentially demyelinated. The brainstem generally has the highest concentration of demyelinating plaques. In the spinal cord plaques are more frequent in the cervical segment. One reason for this distribution is likely related to the tendency for plaques to form around venules and veins and indeed the aforementioned areas have high densities of post capillary venules.

Early in their evolution plaques display active demyelination whilst with time they tend to become inactive. Macroscopically the active plaque displays a pink discolouration and the tissue texture is soft[7]. Microscopically inflammatory cells that contain myelin debris are found throughout the **acute plaque**. More detailed microscopic examination of active demyelination reveals a need for sub-division.

The pathology of the actively demyelinating MS plaque is fundamentally heterogeneous. A confusingly broad range of pathological phenomena has been revealed in the active plaque but the work of Claudia Lucchinetti and colleagues[42] identified four distinct patterns of active plaque pathology. It appears the pathological target (myelin or oligodendrocyte) and the mechanisms of demyelination are distinctly different in subgroups of the disease and at different stages of disease development[42]. Whilst all actively demyelinating lesions exhibit infiltrates of T lymphocytes and macrophages they can generally be segregated based on the distribution of:

- Myelin protein loss.
- Plaque geography and extension.
- Pattern of oligodendrocyte destruction.
- Immunopathological evidence of immunoglobulin and activated complement deposits.

Although full consensus has not yet been achieved, it appears that in the same individual at the same point in time there appears to be homogeneity with regard to the lesional pattern. Lesional pattern is however heterogeneous between individuals and possibly changes over time. Broadly the patterns can separated into those with close similarities to auto-immune encephalomyelitis (patterns I and II) and those associated with oligodendrocyte dystrophy (patterns III and IV)[42].

Pattern I plaques are typically centred on small veins and show sharply demarcated edges with peri-venous extensions. Loss of all myelin proteins from damaged myelin sheaths appears to occur in a simultaneous manner. There is a diffuse immunoglobulin reactivity in the tissue and astrocyte cytoplasm throughout the lesion reflecting blood-brain barrier damage although there is no complement or immunoglobulin deposition. This suggests the destructive process is induced mainly by activated macrophage products such as tumour necrosis factor-α[42]. Pattern I plaques are relatively uncommon and have been found in relapsing-remitting, secondary and primary progressive disease.

Pattern II plaques share the same peri-venous geographical distribution and other features as pattern I plaques. In addition, and exclusively to pattern II, there is prominent deposition of immunoglobulin (mainly IgG) and complement at sites of active myelin destruction. This is associated with degenerate myelin at the active plaque edge and marked immunoglobulin reactivity of myelin degradation products within macrophages. Patterns I and II are associated with a high proportion of re-myelinated shadow plaques. Pattern II was found to be the most common in the identifying research[42] and can be present in any of the main disease sub types and can also be found in chronic MS.

Pattern III lesions are not centred on veins and venules. Instead there is often preservation of a rim of myelin around inflamed vessels within the active lesion. The lesional border is ill defined and merges with the surrounding white matter. This pattern shows a marked loss of oligodendrocytes at the active plaque border often extending into the normal appearing peri-plaque white matter. There are no remyelinated shadow plaques. Whilst the lesions also contain an inflammatory infiltrate composed of T-lymphocytes, macrophages and activated microglia there is

no immunoglobulin or complement deposition. The striking feature of pattern III lesions is the preferential loss of myelin associated glycoprotein (MAG) with relative preservation of other myelin proteins. This is associated with changes suggestive of oligodendrocyte apoptosis. Pattern III lesions are relatively common in acute multiple sclerosis but rarely seen in chronic multiple sclerosis. This pattern of demyelination is not found in primary progressive disease.

Pattern IV lesions are only found in primary progressive disease and are consequently relatively rare. This pattern is associated with a well-demarcated plaque of demyelination with radial expansion. There is no deposition of complement or immunoglobulin, nor any clear evidence of oligodendrocyte apoptosis. There are no remyelinating shadow plaques, nor evidence for a specific myelin protein target.

These different patterns show the marked heterogeneity in the immunopathological profiles of lesions between different MS patients. Recent evidence suggests that the above pathological descriptions also appear to conform with expected therapeutic response[43]. Of 19 patients with multiple sclerosis who had had a lesion biopsy and were treated with plasma exchange moderate or greater neurological improvement was observed in all 10 patients who had pattern II (immunoglobulin and complement deposition) lesions, but none of the 9 patients with either pattern I or III lesions[43].

All of these four patterns show clear evidence of inflammation and lend further support to the extensive literature suggesting that the primary pathology in multiple sclerosis is inflammatory. In 2004, however, a potentially profoundly important study by Barnett and Prineas[3] suggested that the primary pathology in multiple sclerosis may not always, or indeed ever, be inflammation. The authors found extensive **oligodendrocyte apoptosis** in a hyperacute brainstem plaque (17 hours old) that had caused the death and subsequent post-mortem examination of its tragically young host. There was no inflammation in the plaque. This remarkable finding led to the re-examination of autopsy material from other patients who also had relapsing-remitting MS with a rapid and aggressive course. A further nine lesions were found that were essentially identical to the fatal brainstem lesion in the first case. The earliest structural change shared by all these lesions was extensive oligodendrocyte apoptosis in tissue exhibiting early microglial activation but with

little or no infiltrating inflammatory cells. This is unlike any preceding laboratory model of the disease.

This suggests[3] that the earliest lesion in multiple sclerosis may be an apoptotic oligodendrogliopathy that, due to the copious nature of the oligodendrocyte, overwhelms the local mechanisms (microglia) for removing myelin debris. In turn activated macrophages and other inflammatory cells enter the central nervous sytem to augment the clearance of myelin debris. Therefore inflammation may be a secondary and partially adaptive response to oligodendrocyte apoptosis. The cause of any oligodendrocyte apoptosis is not known.

This may suggest that pattern III lesions, which are common in acute MS and display evidence of oligodendrocyte apoptosis in addition to inflammation[42] are in fact a slightly later stage of the pure oligodendrocyte apoptosis and microglial activation.

Some caution should be observed in analysing this study[3]. In particular acute plaques that lead to the rapid provision of autopsy material, or necessitate biopsy, cannot be described as typical in multiple sclerosis. It is possible that these findings in acute, severe multiple sclerosis do not pertain to the disease as a whole.

The individual plaque tends to lose all evidence of active inflammatory activity over time. The **chronic plaque** (commonly defined as one in which there is an absence of inflammatory cells and myelin breakdown products) can show a spectrum of appearances with two extreme forms at either end. The **'closed lesion'** has numerous intact axons although fibrous astrocytic processes have invaded the space previously occupied by myelin. The **'open lesion'** is relatively acellular with a prominent extra-cellular space. It contains few surviving axons and relatively few astrocytes.

Although the white matter plaque, largely for reasons of outlined definition, is the most striking macroscopic pathology in MS it should be remembered that **grey matter** is by no means spared. Approximately a quarter of lesions[44] affect the grey matter, most of these straddle the grey-white matter interface. Cortical lesions are characterized by demyelination as well as axonal damage and neuronal apoptosis[45] although the degree of inflammation appears to be much less in lesions confined to

grey matter than in their white matter counterparts[45;46]. The cortical lesion load appears to be light early in the disease and increase over time. In certain cases the cortical lesion load can involve over a quarter of the entire cortex and be greater than the white matter lesion load[47]. Cortical lesion load is approximately five times greater in progressive than relapsing-remitting disease[48] whilst the white matter lesion load does not seem to differ significantly between these groups. It may therefore be an important contributor towards progressive disease and fixed disability.

(ii) The normal appearing white and grey matter

Whilst MRI techniques[39-41;49-51] have been most widely used in the identification of abnormalities of NAWGM, pathological studies have also demonstrated this phenomenon. Several autopsy studies[52-54] have shown minor but widespread abnormalities in the NAWM from MS patients. These changes include axonal damage, oedema, inflammatory cell infiltrates and astrocytic hyperplasia.

An autopsy study of a patient even in the early relapsing remitting disease phase revealed extensive axonal loss in normally myelinated spinal cord[54]. Axonal loss in the guise of numerous intact but empty myelin sheaths was seen. In addition activated macrophages were observed to be effecting early myelin degradation. Interestingly the axonal loss was restricted to *descending* fibres only and suggests that axonal loss in NAWM may represent antero-grade Wallerian degeneration secondary to remote lesions. Further damage may be propagated by retrograde axonal degeneration resulting in apoptotic neuronal cell body death. In addition axon loss and degeneration, via a loss of trophic factors, may lead to further trans-synaptic axon loss. In this way an 'atrophic positive feedback loop' may lead to widespread damage of the central nervous system in areas remote from obvious inflammatory activity[4;54].

(iii) Axonal loss in multiple sclerosis

MS is historically considered to be a demyelinating disease in which axonal loss, although recognised, was insignificant both pathologically and clinically. It is now recognised that axonal loss is the foundation stone of disability in chronic multiple sclerosis[55]. The development of immunological staining techniques for amyloid precusor protein (APP), a marker of acute axonal damage, revealed that axon damage and loss in the acute plaque was more severe than previously recognised[36;37;55;56]. The extent of acute axonal injury also appears to correlate with the number of inflammatory cells in acute lesions[57]. This finding suggests that axonal loss is an early feature of multiple sclerosis that co-incides with, and is likely the result of, inflammatory demyelination[55].

Axon loss also occurs in chronic, inactive plaques. The rate of axon loss is much lower in chronic than acute plaques[57], but since axonal loss is irreversible and multiple sclerosis is a disease of exceptional longevity it is a potentially more devastating process. Additionally it appears that the slow axonal loss within inactive chronic plaques accelerates slightly in the secondary progressive as compared with the relapsing-remitting disease phase[57]. This may explain the observed paradox of accelerating disability in the face of decelerating CNS inflammation in the progressive disease forms[4]. There is also likely to be significant luxury function within central nervous system pathways[58]. This limits the ability of pathology to cause disability. It is suggested that there is a threshold[55] below which axonal loss does not cause disability. Axonal loss occurs in the acute and chronic plaque, but rather like the hare and the tortoise, it appears that the chronic plaque is often the first to cross the line of irreversible disability.

(4) MRI in multiple sclerosis

The advent of magnetic resonance imaging (MRI), has allowed multiple sclerosis to be studied *in vivo*. Previous x-ray based imaging techniques such as CT were insensitive to all but the most obvious MS pathology. MRI is able sensitively to detect MS plaques[50] and has been able to demonstrate the importance of MRI delineated acute plaques in causing acute focal neurological deficit[50;59;60] and therefore clinical relapse. It has long been assumed that the accumulation of these chronic plaques, and continuing degeneration within them, over time accounts for the progressive deterioration witnessed in later stages of multiple sclerosis. MRI studies have on balance done more to challenge than support this assumption[39;41;49;61]. The concept of multiple sclerosis being a multi-focal disease of the central nervous system may only be correct in its earliest stages. The major utility of MRI in multiple sclerosis is diagnostic[15], its value in prognosis and as a surrogate marker for disability is less clear[62].

As with histopathology, there is a functional heterogeneity to the plaques which MRI techniques are not able fully to reveal. It should be remembered that MRI depends not on the functional state of the nerve fibres but on the amount and distribution of water in the intra- and extra-cellular spaces in the affected area.

(i) MRI of MS plaques

The evidence for relapse being accompanied by appropriate changes on an MRI scan is strong. There is an excellent correlation between the development of symptomatic focal neurological dysfunction and the development of an **acute plaque** in the relevant pathway of the CNS. In 10 patients with acute optic neuritis studied[59] with T_1-weighted MRI, all 11 clinically affected nerves enhanced with gadolinium implying breakdown of the blood-optic nerve barrier and inflammation. Gadolinium enhancement was associated with abnormal visual acuity, colour vision, retro-orbital pain on eye movement, afferent pupillary defect and decreased visually evoked responses (VERs). Repeat MRI 4 weeks later revealed gadolinium enhancement had stopped in 9 of the 11 nerves and this corresponded with clinical improvement.

Further evidence for acute lesions causing relevant focal neurological deficit comes from a study[60] of 121 patients with non-compressive spinal cord syndromes who were imaged with MRI. There was a good correlation between the neurological deficit and location of lesion. This was highlighted by the association between lesions in the cervical dorsal root entry zone of patients exhibiting the 'useless hand of Oppenheim'. Another important study[50] showed that 35 of 40 patients with MS who presented with an acute brain stem syndrome had a lesion demonstrated in the brainstem by MRI. There was a good correlation between precise site of lesion and the clinical picture in the case of cranial nerve palsies, the one-and-a-half syndrome and internuclear ophthalmoplegias (INO), although the last observation should be tempered by the high frequency with which lesions of the floor of the 4th ventricle were found such that a lesion in the region of the medial longitudinal fasciculus could be found in patients without an INO.

Whilst clinical dysfunction is often accompanied by appropriate lesion formation on MRI the reverse is not true. Clinically silent plaques are approximately ten to fifteen times as common as symptomatic plaques in multiple sclerosis[7;63]. Whilst this may be in part due to lesions forming in clinically irrelevant locations this is not the whole answer as MRI frequently discloses asymptomatic lesions in clinically eloquent areas such as the spinal cord[64]. Family studies have revealed MRI changes typical of multiple sclerosis in unaffected relatives of MS patients[65]. This is not just an MRI phenomenon. Post mortem evidence has revealed that the finding of the pathological features of multiple sclerosis in a patient who was asymptomatic in life is not uncommon[66]. This is not always due to lack of clinical eloquence of involved pathways: an extensive demyelinating lesion has been reported in the spinal cord of a patient asymptomatic in life[67]. For obvious reasons it is difficult to accurately assess the true incidence of 'asymptomatic' multiple sclerosis and more difficult still to know whether this is truly asymptomatic or merely pre-symptomatic MS[68]. The very concept of asymptomatic multiple sclerosis highlights that plaques are not synonymous with clinical dysfunction.

The relationship between the **chronic plaque** and neurological dysfunction is not as obvious. Studies which have compared the total volume of brain occupied by T_2

lesions and compared this with clinical disability have variously found correlations ranging from none[69] to modest[70] and overall is felt to be weak[71]. T_2-weighted imaging for assessment of multiple sclerosis pathology is therefore limited by its poor specificity for identifying dysfunctional plaques and non plaque white matter.

MRI has revealed marked differences between primary and secondary progressive multiple sclerosis. In one study[72] of 12 secondary and 12 primary progressive MS patients who were otherwise well matched there were an average of 18.2 new lesions per year in the secondary progressive group whilst there were only 3.3 new lesions per year in the primary progressive group on brain MRI. Another study of 91 patients found the brain T2 lesion load in primary progressive disease to be lower than in either secondary progressive or relapsing remitting disease[73]. MRI techniques suggest[74] that the spinal cord is more heavily involved than the brain in primary progressive multiple sclerosis. This spinal cord damage in primary progressive MS, however, is probably no greater than that seen in disability matched secondary progressive disease[75].

Hypointense T_1 lesions, or 'black holes' do correlate with more severe tissue disruption, including axon loss and demyelination[76]. Initial studies[77] showed a good correlation between T_1 lesion load and disability, however subsequent larger studies have found only a weak link[78].

This dissociation between disability and conventional MRI occurs with different disability rating scales[20]. Thus MRI suggests that disability is largely unrelated to chronic lesion load and casts doubt on the theory that multiple sclerosis is a chronic multi-focal CNS disease. Therefore we need to consider the MRI evidence against the two remaining components of the diseased CNS: normal appearing CNS tissue (NAWGM) and disappearing CNS tissue (atrophy).

(ii) MRI of normal appearing CNS tissue

Modern MRI techniques, such as magnetization transfer ratio (MTR), magnetic resonance spectroscopy (MRS) and diffusion weighted imaging (DWI) can detect biochemical and structural change of the CNS invisible to conventional MRI. This

allows the in vivo quantification of the involvement of NAWGM in MS[61]. Region of interest (ROI)[41;79;79-83] and histogram[80;81] studies have shown subtle degenerative change and altered metabolism within NAWGM in all of the MS sub-types. These changes are evident even in clinically isolated syndromes (CIS) suggestive of MS[41;84;85] providing good evidence that changes in NAWGM may not be secondary to discrete lesions. Abnormalities of NAWGM are however more marked in progressive disease compared to relapsing-remitting disease[86;87]. Primary and secondary progressive disease displays similar NAWGM abnormalities[75;88]. Unlike most conventional MRI techniques, MTR of the NAWGM can predict the accumulation of disability over a subsequent five-year period[89;90]. MRS has revealed that there are developing abnormalities of areas of NAWGM that subsequently develop into classical MS lesions[91]. MTR, MRS and DWI have also shown that regional abnormalities in the pyramidal tracts[92], cerebellum[93] and optic nerve[94] produce clinically relevant impairment.

(iii) The role of disappearing white and grey matter in multiple sclerosis (atrophy)

It is easy to overlook what isn't there. Whilst the disability ensuing from an amputated leg is easy to envisage the concept becomes less obvious, although no less important, when considering the spaces formerly occupied by axons and myelin sheaths. It is slightly complicated by the partial restoration of volume that may result from remyelination, gliosis and oedema. Atrophy of the CNS as measured by MRI does correlate well with disability in multiple sclerosis[95-97]. In keeping with the observations of axonal loss, it appears that atrophy of both plaque matter and NAWGM occurs[37]. There is evidence that plaques atrophy completely[98] (personal communication – Trapp BD) which may partly explain the relatively poor relationship between lesion load and disability at a given point in time[69]. In turn this makes the problem of identifying clinically symptomatic lesions for therapeutic purposes[99] more difficult: the clinically relevant lesion may have disappeared but left its resultant disability behind. In these cases areas of focal atrophy[100] may be the only clue to a pre-existent plaque.

In **conclusion** MRI studies of MS have confirmed or revealed the following:

- Clinical relapse is often associated with relevant acute lesion formation.
- Lesion formation is infrequently associated with clinical relapse.
- The lesion load is only weakly related to chronic disability.
- Atrophy of the CNS is closely related to disability.
- The normal appearing white and grey matter is structurally and metabolically abnormal, even at the earliest stages of disease and these abnormalities correlate well with disability.

Therefore it may be reasonable to conclude that normal appearing white and grey matter, and disappearing white and grey matter (atrophy) are more relevant to disability in MS than abnormal appearing white and grey matter (lesions).

(5) The treatment of multiple sclerosis

The concept of multiple sclerosis as a primary inflammatory multi-focal disease of the central nervous system has not been strengthened by the developing pharmacology of MS. An increasingly sophisticated array of pharmaceutical agents has yet to convincingly slow or stop long-term disease progression. This is despite clear evidence of a reduction in inflammatory activity in the central nervous system.

Corticosteroids decrease inflammation and shorten relapse duration but do not appear to have any long-term beneficial effect in multiple sclerosis[7], with the possible exception of improving spasticity temporarily in chronic progressive disease. Similarly steroid sparing immunosuppressive drugs such as **azathioprine**[101] and **methotrexate** have had a disappointing risk:benefit ratio in MS. A common problem has been drugs that may confer a short-term benefit that is unsustained with prolonged follow up, **sulphasalazine**[102] being one example. Some treatments that are not presently considered to be practical or effective in multiple sclerosis may be useful in as yet unidentified sub-groups of MS patients. This is highlighted by the discovery that **plasma exchange**[43] appears to be effective in MS patients with pattern II lesions but not pattern I or III. An evolving knowledge of MS may see previously ineffective drugs become effective when targeted appropriately.

The spread of the **Acquired Immunodeficiency Syndrome** (AIDS) in the 1980s provided further evidence of a dissociation between inflammation and disability in multiple sclerosis. Although clearly not an intended treatment for MS, AIDS through its pathological ablation of immune function might have been expected to favourably affect MS. This was not the case. MS continued to progress in men whose immune systems had been seriously impaired by AIDS[103].

The immunomodulatory drugs **beta-interferon** and **glatiramer acetate** have been shown in the 'pivotal' trials to be effective in reducing the relapse frequency by about one third[8;104-107] at two years. Two of these trials have claimed a statistically significant effect on disability progression[8;107]. A systematic review[108] and meta-analysis of the beta-interferon trials has produced rather more modest claims for the effects of these drugs. Despite access to 7 trials and complete data on 1215 patients

this study was only able to conclude that the beta-interferons were significantly associated (p=0.04) with a relative risk of relapse of 0.73 compared to placebo. There was no effect of beta-interferon on preventing disability[108]. Whilst it is not clear if this represents a failing of beta-interferon or trial methodology, it is clear that there is no good evidence that these drugs prevent disability in the longer term[9].

The effect of beta-interferons on MRI lesion activity is certainly greater than their clinical effect[105;107] and is in keeping with the known poor association with lesion load and disability[69].

The role of immuno-modulatory drugs was taken to an extreme with the potent lymphocyte depleting antibody **Campath-1H**[12]. In 25 patients with secondary progressive multiple sclerosis, treatment with Campath 1H did produce a very impressive reduction in gadolinium enhancing lesions and T_2 lesion volume. However, it did not reduce T_1 hypointense lesions and rate of CNS atrophy compared with an admittedly small control group of 4 patients. Perhaps most importantly the reduction in gadolinium enhancement and T_2 lesion load did not reduce disability progression compared with controls. The only MRI indices correlated significantly with Expanded Disability Status Score (EDSS) in this study were spinal cord atrophy and infratentorial T_1 to T_2 ratio. There is some evidence to suggest that immunomodulatory treatment of the early stages in MS may be effective in slowing disability progression[109], whilst the progressive stages of the disease are likely less dependent upon inflammation, and therefore less amenable to immunomodulation.

Natalizumab, an alpha4 integrin antagonist has a marked effect on new MRI lesion formation in MS (92.7% reduction in new lesion formation compared to placebo) and halves the number of patients experiencing relapses[95]. Despite further promising results Natalizumab has been setback indefinitely by the co-occurrence of progressive multi-focal leukoencephalopathy (PML)[110;111].

From this we can see that despite the availability of potent immunomodulatory drugs that have confirmed and substantial effects on MRI markers of neuro-inflammation in MS we have not been able to demonstrate a sustained effect on disability

progression[9]. This suggests the role of inflammation in producing disability in MS may not be primary, and furthermore may not be entirely deleterious.

It seems counter-intuitive to suggest that inflammation might be anything other than deleterious, however whilst inflammation in multiple sclerosis clearly does cause CNS tissue destruction it has also been shown to produce effects beneficial to recovery[26] and repair of the central nervous system. Inflammation is known to stimulate remyelination in areas of chronic demyelination[27]. Whether inflammation overall in multiple sclerosis is a good or bad phenomenon is unknown and it is likely to be heterogeneous between individuals. Clearly in aggressive disease, such as the Marburg variant, the negative aspects of inflammation probably exceed any benefits. More difficult to say is whether patients with benign, or even asymptomatic disease are actually benefited by cerebral inflammation. For this to be the case it would be likely that MS is due to an alternative primary pathology and that inflammation is an adaptive response to this primary pathology. Viral infection[112] or failure of natural neuro-regenerative mechanisms leading to uncontrolled apoptosis[3] may necessitate the involvement of the immune system.

If inflammation was overall an evolutionarily preserved adaptive mechanism to ameliorate an as yet unidentified primary pathology then one might expect to see long term advantage in patients experiencing an appropriate level of CNS inflammation (benign or asymptomatic MS) as compared with those experiencing too much (relapsing-remitting and Marburg variant) or too little (primary progressive).

This returns us to our natural history studies that suggest that relapses and, by extension, inflammation may be associated but not causally related to disability progression[11]. Technically proving a non-causal relationship over a disease that lasts decades is challenging. However if it were to be shown that in a significant population of MS patients the *quality* of the preceding relapses do not match the *quality* of the subsequent disability then it would constitute a powerful argument to suggest that relapses, and inflammation, are not the true problem.

(6) Summary

Our current understanding of chronic disability in multiple sclerosis is dominated by intuitively held assumptions of a strong relationship to acute inflammatory relapses. Treatments which prevent relapses are assumed to have useful long term benefit in reducing disability; we look at MRI scans of chronic MS patients and try to establish which lesion might be responsible for some aspects of their disability; we even plan future myelin repair therapies on the basis of injecting cells into chronically 'disabling' lesions. And yet even the brief consideration outlined above casts doubt on this fundamental and near-universal assumption. The evidence from natural history, pathological and radiological studies increasingly suggest the relationship between relapse, inflammation, and chronic disability is non-linear and complex in MS. Consequently the contribution of acute lesions and relapses to progressive neurological deficits is open to question. This has been further emphasised by the continuing failure of novel immuno-modulatory therapies to have a proven effect on disease progression and disability. On the basis of this para-clinical evidence, a purely clinical study is merited to examine long held assumptions regarding the relationship of relapse to disability. This is what I have attempted.

Chapter 2: A cross sectional survey of neurological examination findings in 150 hospital based patients with multiple sclerosis

Aim: To describe in detail the neurological deficits at prevalence in a defined population of patients with multiple sclerosis.

Introduction

Multiple sclerosis, in common with many chronic diseases, is primarily a disease of morbidity[113] rather than mortality. The morbidity of multiple sclerosis principally occurs in the form of physical disability. There are many different techniques for assessing disability[19;114;115] in multiple sclerosis. Whilst each has distinct qualities on the whole they seek to give a quantitative assessment of disability. Often, despite the tremendous clinical heterogeneity of multiple sclerosis, an individual's disability is expressed in terms of a single figure score. Whilst reductive disability scales are fundamentally necessary in order to bring structure to natural history and therapeutic studies they provide only limited information. For instance an Expanded Disability Status Score (EDSS) of 6 means that a patient is dependent upon a walking stick. It makes no comment on whether this is because they are weak, ataxic (sensory or cerebellar), blind or perhaps a combination of these factors.

McAlpine's original schemata[116] demonstrating the temporal course of multiple sclerosis is an accurate representation of how we traditionally perceive multiple sclerosis over time (see figure 1-1). It still forms the basis of patient and undergraduate education in multiple sclerosis. It starts with individual spikes in disability that often resolve completely. Sometimes however these spikes in disability do not resolve and this forms the basis of step wise disability progression throughout the relapsing remitting phase. With time relapses become less frequent and often give way to a relentless phase of progressive disability. Key to this percept is that the relapse rate is a key component in the formation of long-term disability in multiple sclerosis[117].

Thus multiple sclerosis was perceived as a relatively simple inflammatory disease of the central nervous system. It was widely felt that episodes of focal inflammatory demyelination produced acute relapses and that the burden of these lesions over time led to an inexorable progression of disability. If we were able to stop this inflammation then the disease should be prevented from causing further disability.

These theoretical benefits of anti-inflammatory and, more recently, immuno-modulatory therapies continue to be substantially greater than their observed practical benefits. Corticosteroids have an effect on relapse severity but not prospective relapse rate or long term disability. Beta-interferons and glatiramer acetate have a prospective effect on relapses but conclusive proof of long-term disability prevention is still lacking. The anti-inflammatory strategy has been taken to greater extremes with the monoclonal antibody Campath-1H[12] which conclusively inhibited the inflammatory components of multiple sclerosis, but not progression of disability in secondary progressive patients. In short we can dramatically affect inflammation in multiple sclerosis but, to date, this has not translated into long-term disability prevention at a population level.

Large natural history studies[10;11] have not shown the relationship between number of relapses, the degree of recovery from relapses and the rate of disability progression that one would intuitively expect from a primary inflammatory disease of the central nervous system.

Histopathological studies have revealed four different patterns of demyelination in multiple sclerosis[42;118]. These are (I) T cell/macrophage mediated; (II) antibody/complement mediated; (III) oligodendrocyte dystrophy with myelin protein dysregulation and oligodendrocyte apoptosis; (IV) primary oligodendrocyte degeneration with features similar to viral infection or toxic oligodendrocyte damage. Whilst these processes are heterogeneous within patients, pattern IV was only observed in cases of primary progressive disease. It is unlikely all 4 types of demyelination will be susceptible to the same therapeutic agent, unless of course we are merely observing the evolution of demyelination in a 'snap shot' fashion. If different types of demyelination exist perhaps they produce different clinical

phenotypes that will ultimately allow more targeted selection of therapeutic agents than is presently possible.

A further recent pathological study suggested that different tracts within the nervous system of the MS patient sustain damage at different rates[119]. This is compatible with clinical experience that certain tracts within the nervous system, for example the optic nerves and medial longitudinal fasciculus, seem preferentially susceptible to acute relapses in multiple sclerosis.

So there are variable types of demyelination and also perhaps variable resistances or susceptibilities of the different central nervous system pathways. Likely therefore there are qualitative differences in the way that different types of impairment and disability form. The secondary progressive phase for instance is defined purely in terms of disability progression. It is not clear from the literature whether all neurological pathways enter the secondary progressive phase at the same stage or whether we are in fact merely observing the stage at which pathways more crucial to disability, such as the corticospinal tracts, begin to degenerate. Quantitative disability studies tell us that primary and secondary progressive disease progress at the same rates[10;120] despite apparent differences in radiological studies in these patients. One group[69] has reported profound MRI activity differences among several clinical categories of patients. Primary progressive patients had the lowest rate of activity at 3.3 new T_2 lesions per patient per year. Next was benign MS at 8.8, followed by relapsing remitting MS and secondary progressive MS at 17.2 and 18.2 new lesions per year.

A 'complete' neurological examination is used to examine the majority of patients who have multiple sclerosis at one stage or another. Whilst the term 'complete' neurological examination is unlikely to have identical connotations between all neurologists we believe there is a significant degree of overlap between the various interpretations. Although there is little formal evidence base one assumes through its natural evolution that the findings of this neurological examination are useful. It is through this anecdotal experience that our perceptions of disease are largely formed. But is our anecdotal experience of multiple sclerosis entirely accurate or are we subject to recall bias? We can all remember a relapse in a patient with multiple

sclerosis that has clearly led to prolonged disability. So why then do large natural history studies tell us that disability is largely inconsequent on previous relapses? Perhaps our anecdotal observations are correct but incomplete. If there were a large proportion of patients whose relapses weakly preserved long-term function they could negate the effects of a small but highly visible minority with marked dysfunction in response to relapse. Are we subject to recall bias that is eliminated to a degree in these natural history studies[10;22] or does measurement of disability scores allow important long-term qualitative effects of relapses to be overlooked?

Whilst a long term prospective study of clinical signs in multiple sclerosis would have been ideal it is also clear that the chronic disease course requires more than one research generation for follow up studies. A cross sectional approach to clinical signs however does mean that all the clinical data is essentially prospective. We were unable to find previous work detailing the systematic findings of a complete neurological examination in a population of patients with multiple sclerosis. Numerous previous works[17;113;121;122] have reported summary findings from clinical examinations in these patients but the manner in which these studies summarise their findings is frequently heterogeneous.

Our aim was to systematically report the findings of a complete neurological examination in a population of multiple sclerosis patients and identify whether there were predictable patterns in which certain clinical signs become evident. For instance: do individual clinical signs become significantly more evident with increasing disease duration or whether the patient has entered the secondary progressive phase? Are the clinical findings in primary and secondary progressive disease the same or are there important differences that are not revealed by cumulative disability scores? What effect does the patient's age and sex have on the appearance of clinical signs? Do all clinical signs obey the same rules or are they responding to different pathophysiological cues?

The answers to these questions are critical to further our understanding of the manner in which impairment, the substrate of disability, accumulates in patients with multiple sclerosis. If individual clinical signs all appear in response to the same constitutional factor then there is likely to be a common disabling pathogenetic

process, possibly susceptible to a single therapeutic agent, as the basis for all disability. The obverse is also likely to be true.

Methods

Between 2002 and 2004 151 patients with multiple sclerosis were referred to Frenchay hospital neurology department to be assessed as to their suitability for disease modifying drugs in multiple sclerosis as part of the United Kingdom Governments Risk Sharing scheme[31;32;123]. Referrals were accepted from consultant neurologists and were limited to patients with definite multiple sclerosis according to the McDonald criteria[15], aged 18 years and over but were otherwise unselected. In particular, patients in whom it was immediately evident that they were not serious candidates for disease modifying drugs, such as those without any relapses or with advanced disability, were not excluded from assessment. Any patient considered to be in relapse at the time of initial assessment was re-assessed at a later date when relapse recovery was considered complete. One patient was excluded from the analysis as they declined physical examination. The demographic data, including sex, age and disease duration at the time of assessment of these patients was evaluated by interview and examination of their case records. A full neurological examination as part of an assessment of Expanded Disability Status Score (EDSS)[19] was also recorded. All details of the patients demographic and EDSS examination, ranging from detailed modality and site-specific findings through the individual Functional Score Systems (FSS) to the overall EDSS score were entered into a password secured computer database (Microsoft Access). The forms used for data recording can be seen in Appendix 1.

The computer database was discussed with and kept in accordance with North Bristol NHS Trust Data Protection regulations. Ethical approval for this study was obtained from Frenchay Hospitals Local Research and Ethics committee (Frenchay LREC/2003/31). All patients gave their written consent for their clinical data to be used in this study.

All assessments were performed by either the author or Dr Janice Burrow, both of whom have several years of experience in taking a history and performing neurological examination.

Statistical analysis

Statistical analysis in this study include standard methods of descriptive statistics, as well as binary logistic regression to analyse the effects of sex, age, disease duration and disease subtype on the presence of various clinical signs. Data analysis was performed using SPSS version 12 (SPSS inc., Chicago, IL) statistical package. Based on the non-parametric distribution of scores in ordinal ranks within many Kurtzke Functional Score System sub-categories including a frequent large proportion of zeros it was decided that linear regression was inappropriate. The need for multivariate analysis necessitated against the Kruskall-Wallis test. Binary logistic regression was preferred to ordinal logistic regression based on the size of the study population. For purposes of binary logistic regression the absence of a clinical sign was scored as 0 whilst the presence of a clinical sign was scored as 1. The comparator groups for the binary logistic regression included female sex and secondary progressive disease. We considered the role of multiple observations increasing chances of type 1 errors but decided against making correction for this as observations are being made on different impairment types, and although we accept there may be some associations between individual clinical signs these are partially compensated for by the inclusion of the qualitative predictors (sex, age, disease duration, disease sub-type) in the model. Therefore we have reported $p \leq 0.05$ as statistically significant.

Results

Abbreviations:

PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
RAM	Rapid alternating movement
OR	Odds Ratio
EDSS	Expanded Disability Status Score
FSS	Functional Systems Score
SA	Shoulder Abduction
EF	Elbow Flexion
EE	Elbow Extension
WF	Wrist Flexion
WE	Wrist Extension
HF	Hip Flexion
KF	Knee Flexion
KE	Knee Extension
ADF	Ankle Dorsi-Flexion
APF	Ankle Plantar-Flexion

(1) Demographic and disability data

Table 2-1: Gender, disease sub-type, age and disease duration of the 150 study patients with multiple sclerosis

Demographic feature		Male	Female	RRMS	SPMS	PPMS	All
Sex	Female			78	31	7	116
	Male			25	7	2	34
Disease Duration at assessment (years)	Mean	7.2	9.7	8.2	12.1	7.9	9.2
	Range	1.33-23.17	0.58-39.67	0.58-33.92	1.33-39.67	2.91-16.5	0.58-39.67
Age (years)	Mean at assessment	38.8	40.1	37.9	42.9	48.6	39.8
	Mean at onset	31.6	30.4	29.7	30.8	40.7	30.6
	Range at assessment	18-56	19-72	19-64	18-63	36-72	18-72

Figure 2-1: The distribution of sex and disease subtype amongst study cohort (n=150)

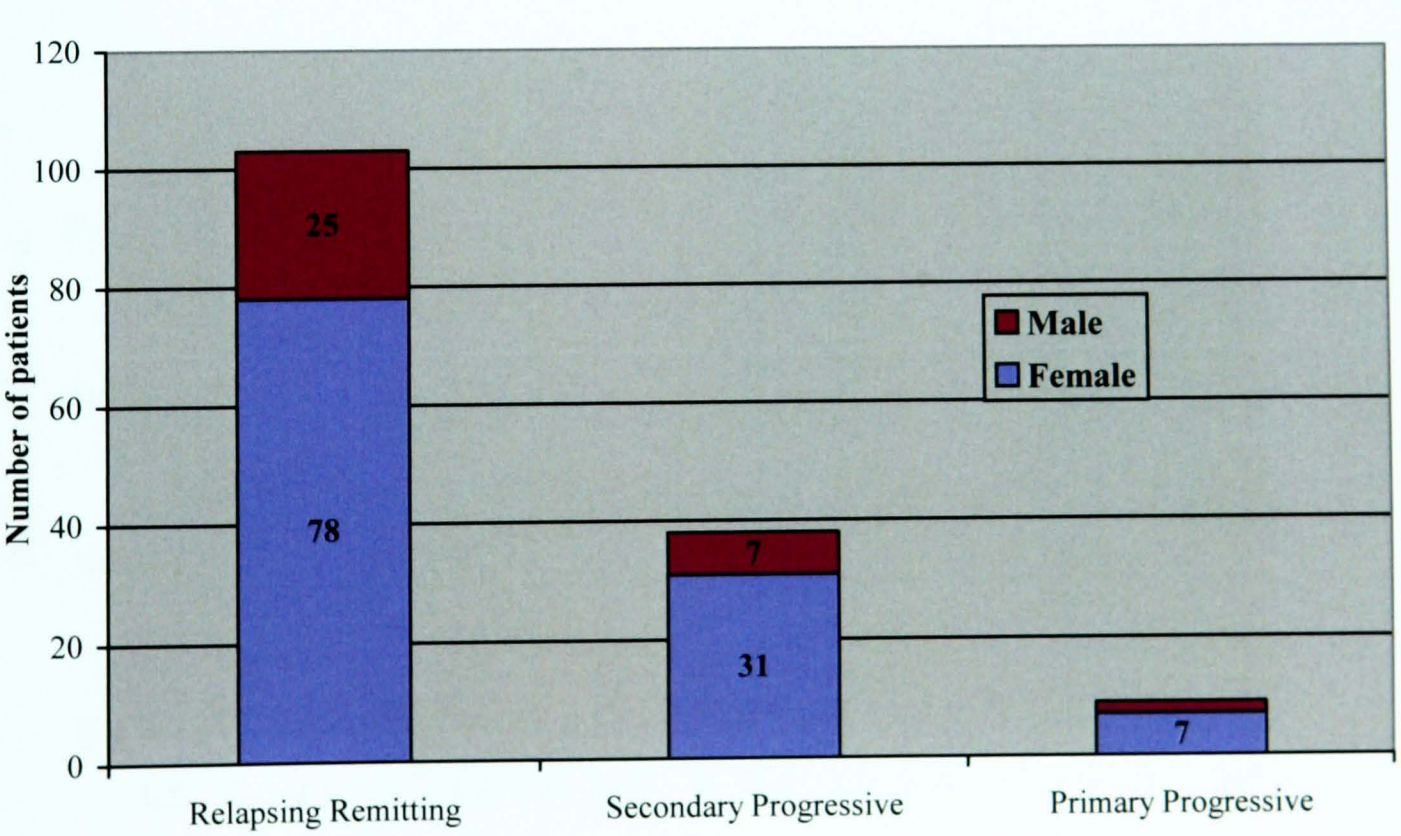


Figure 2-2: Mean age of patient sub-groups at disease onset and assessment (n=150)

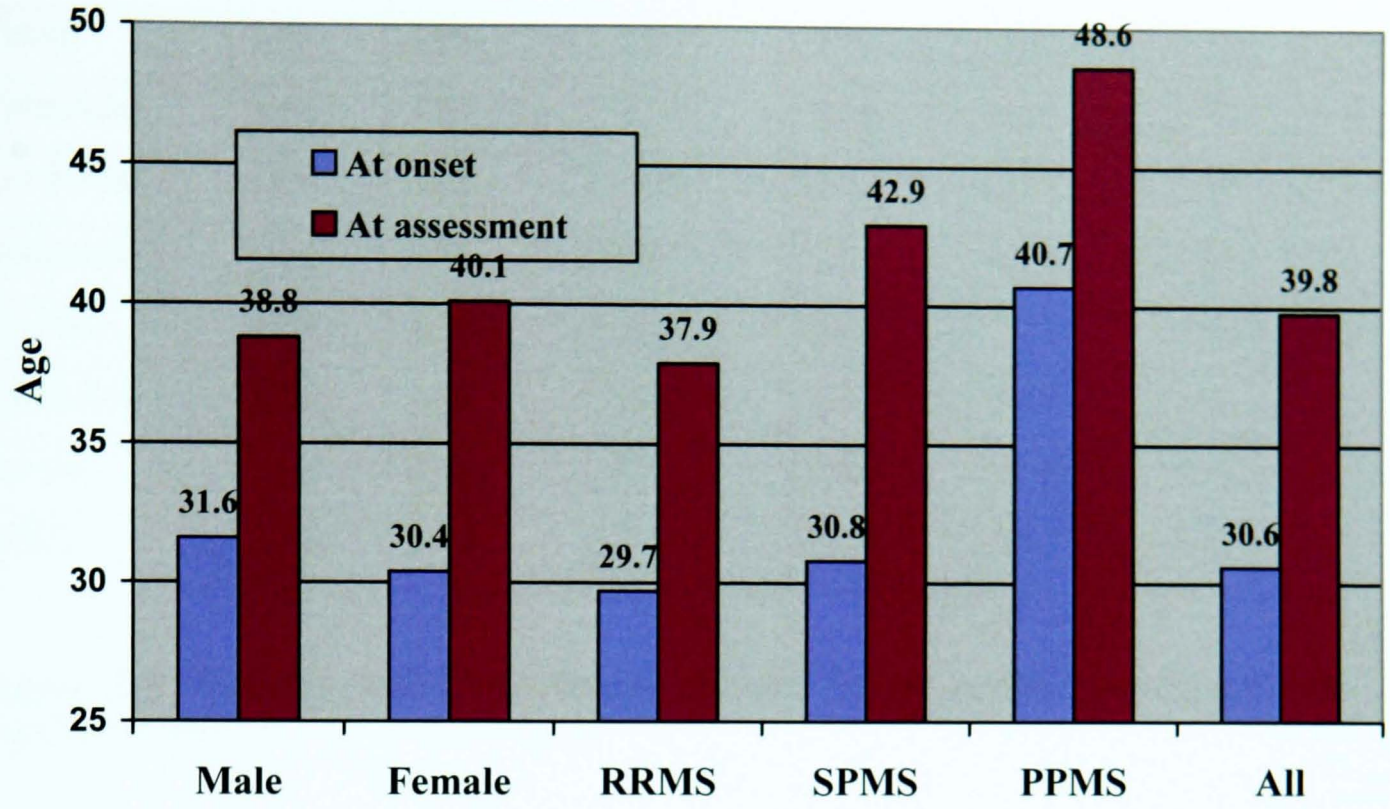


Figure 2-3: Distribution of EDSS scores according to disease sub-type (n=150)

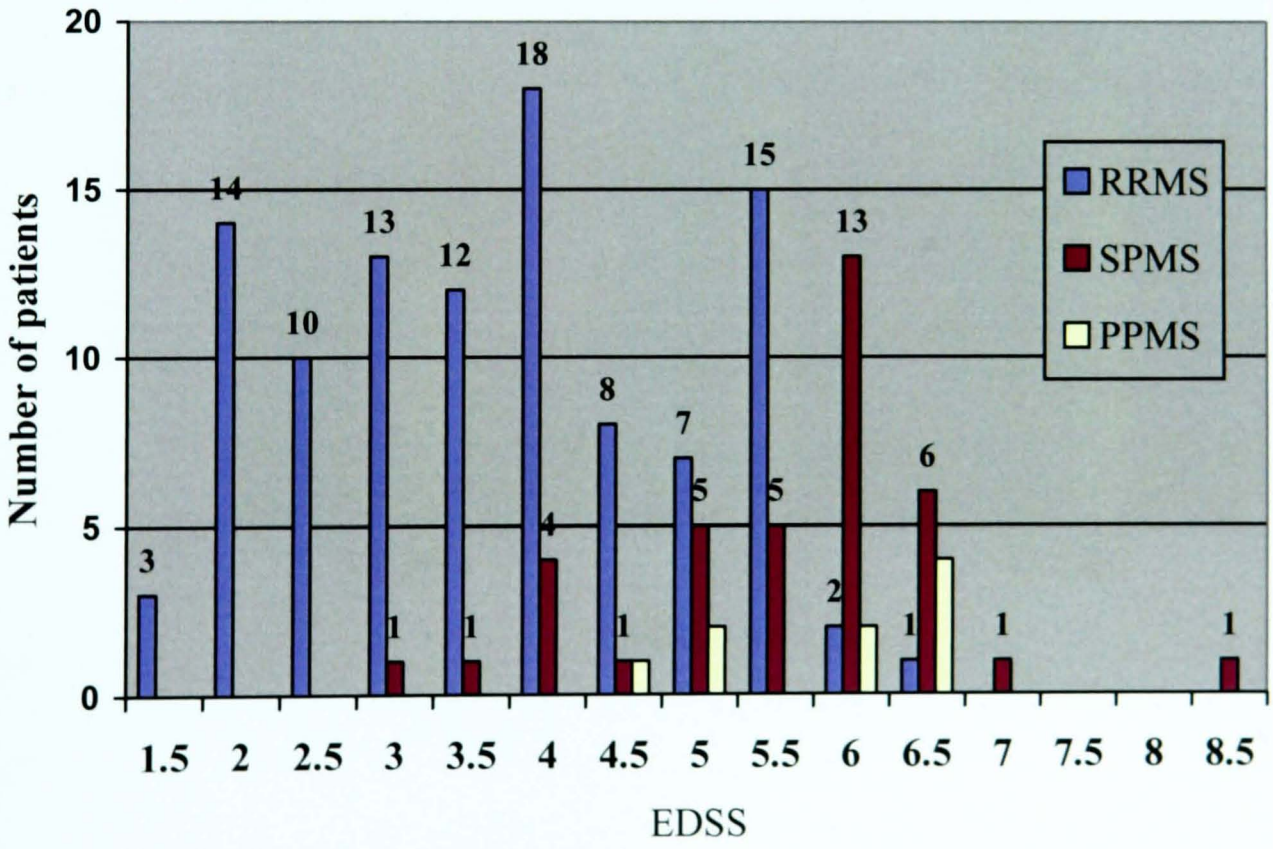


Table 2-2: Mean EDSS and FSS amongst 150 patients with multiple sclerosis

	Male	Female	RRMS	SPMS	PPMS	All
Visual	1.47	1.01	1.09	1.53	0.89	1.11
Pyramidal	1.68	1.83	1.34	2.68	3.11	1.79
Cerebellar	1.94	1.81	1.52	2.53	2.55	1.84
Brainstem	1.06	1.09	0.9	1.53	1.33	1.09
Sensory	2.38	2.54	2.31	3.02	2.56	2.50
Sphincter	1.29	1.43	1.24	1.71	1.89	1.4
Mental	0.56	0.46	0.42	0.63	0.55	0.48
EDSS	3.86	4.44	3.71	5.58	5.83	4.31

Figure 2-4: Selected Mean Functional Systems Scores across the disease sub-types (n=150)

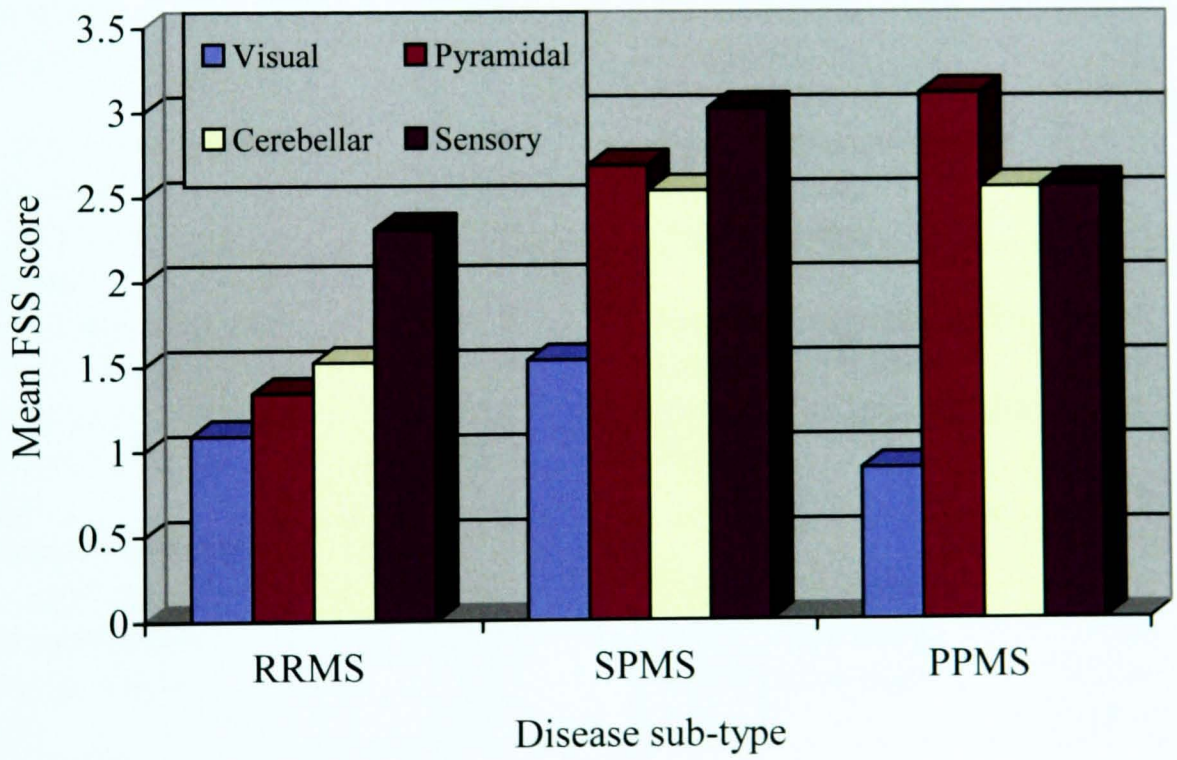


Table 2-3: Comparative frequency of clinical signs in multiple sclerosis from 2 previous studies

Clinical signs in 301 prevalent patients in South Glamorgan by examination [113]	% frequency	Clinical signs in 557 patients in North-East Scotland[122]	% frequency
Visual Function:			
Impaired acuity	72.4	Not reported	
Impaired colour vision	59.8		
Field defect	25.9		
Disc pallor	41.5		
Normal	08.0		
Brainstem function:			
Nystagmus	48.2	Nystagmus, horizontal	40.6
Eye movement disorder	23.9	Nystagmus, ataxic	19.0
Facial weakness	09.0		
Dysarthria	21.3	Dysarthria	21.2
Dysphagia	05.6		
Other	13.0		
Normal	44.9	Normal	19.4
Tone and Power:			
Increased tone	56.5		
Monoparesis	06.6	Monoparesis	21.2
Hemiparesis	04.3	Hemiparesis	12.4
		Paraparesis	27.3
Para- and mono-paresis	14.9	Para- and mono-paresis	15.3
Quadriparesis	25.9	Quadriparesis	7.5
Normal power	25.9	Normal power	16.3
Sensation:			
Impaired spinothalamic	49.2	Impaired spinothalamic	32.0
Impaired vibration	61.5	Impaired vibration	62.5
Impaired proprioception	38.5	Impaired proprioception	33.1
Impaired two point	42.2	Normal	
Normal	21.6		19.4
Cerebellar function:			
Upper limb ataxia	46.8	Upper limb ataxia	58.2
Lower limb ataxia	25.2	Lower limb ataxia	39.0
Combined ataxia	17.3	Combined ataxia	29.6
Normal	36.2	Normal	32.4
Tendon reflexes:			
Clonus	16.0	Clonus	47.6
Hyperreflexia	59.1	Hyper-reflexia	92.8
Hyporeflexia	14.0		
Normal	14.0		

Table 2-3 (cont): Comparative frequency of clinical signs in multiple sclerosis from 2 previous studies

Clinical signs in 301 prevalent patients in South Glamorgan by examination [113]	% frequency	Clinical signs in 557 patients in North-East Scotland[122]	% frequency
Sphincteric function:			
Urinary hesitancy +/- urgency	38.5	Hesitancy, frequency or precipitancy of micturition	38.1
Urinary incontinence	15.3	Urinary incontinence	17.8
Bowel dysfunction	7.6	Bowel dysfunction	6.8
Normal	37.9	Normal	43.6
Cerebral involvement:			
Mood	26.9	Euphoria	17.4
		Depression	7.5
Intellect	13.3	Intellectual deterioration	
		Seizures	6.1
Seizures	4.0	Normal	1.8
Normal	59.8		69.5

(2) Incidence of clinical signs in this study cohort (n=150)

Table 2-4: Incidence of specific clinical signs amongst the study cohort (%)

System	Sign	Site	Male	Female	RRMS	SPMS	PPMS	All
Pyramidal	Increased tone	Arm	13.2	4.3	1.5	17.1	16.7	6.3
		Leg	27.9	27.6	17.0	47.4	66.6	27.7
	Weakness	SA	7.4	4.7	2.91	10.5	11.1	5.3
		EF	10.3	3.0	3.4	7.9	5.6	4.7
		EE	8.8	3.0	1.9	7.9	16.7	4.3
		WF	8.8	4.3	3.9	9.2	5.6	5.3
		WE	8.8	6.9	5.8	11.8	5.6	7.3
		HF	30.9	32.8	21.4	54.0	66.7	32.3
		KF	29.4	28.0	18.9	44.7	66.7	28.3
		KE	19.1	10.3	6.3	21.1	44.4	12.3
		ADF	20.6	16.4	8.3	32.9	55.6	17.3
		APF	14.7	11.2	4.9	25.0	38.9	12.0
	Brisk Reflexes	Bicep	13.2	11.6	10.2	14.5	22.2	12.0
		Supin.	16.2	10.3	8.7	17.1	22.2	11.7
		Tricep	8.8	9.5	6.8	13.2	22.2	9.3
		Knee	26.5	20.7	17.0	31.6	38.9	22.0
		Ankle	20.6	9.1	11.2	11.8	16.7	11.7
	Extensor Plantar response		44.2	40.1	24.3	75	88.9	41
Sensation	Superficial	Arm	44.1	34.1	28.6	56.6	38.9	36.3
		Leg	42.6	38.4	34.4	57.9	16.7	39.3
	Vibration	Arm	63.2	75.9	66.5	88.2	83.3	73.0
		Leg	76.5	90.5	81.6	100	100	87.3
	Proprioception	Arm	4.4	4.3	1.9	11.8	0	4.3
		Leg	11.8	7.3	4.4	27.6	5.6	10.3
	Rhomberg's test +ve		17.6	20.7	6.8	50	33.3	19.3
Cerebellar	Dysmetria	Arm	27.9	18.1	16	26.3	44.4	10.3
		Leg	35.3	30.6	21.8	50	66.7	31.7
	Dysdiadochokinesis	Arm	26.5	15.9	13.1	25	50	18.3
		Leg	42.6	28.9	21.3	50	77.7	32
	Resting Tremor	Arm	2.9	3.4	2.9	5.2	0	3.0
		Leg	2.9	0	0	2.6	0	0.7
	Gait Abnormality	Eyes open	55.9	60.3	42.7	94.7	100	59.3
		Eyes closed	79.4	78.4	70.9	94.7	100	78.7
Visual	Acuity (≥6/9)		30.9	24.1	18.9	39.5	44.4	25.7
	Field Defect		10.3	1.3	2.9	5.3	0	3.3
	Scotoma		5.9	12.1	10.7	13.4	5.6	10.7
	Optic Atrophy		32.4	31.9	28.2	47.4	11.1	32.0
Brainstem	Eye movements		17.6	8.6	7.8	18.4	11.1	10.7
	Nystagmus		29.4	12.9	13.6	21.1	33.3	16.7
	Trigeminal sensory deficit		29.4	28.4	25.2	42.1	11.1	28.7
	Facial weakness		5.9	2.6	2.9	5.2	0	3.3
	Hearing loss		11.8	5.2	4.9	10.5	11.1	6.7
	Dysarthria		14.7	18.1	11.7	28.9	33.3	17.3
	Dysphagia		5.9	12.1	4.9	23.7	22.2	10.7
	Tongue RAM		8.8	6.9	2.9	15.8	22.2	7.3
Sphincter	Urinary Urgency		55.9	57.7	50.5	65.8	100	57.3
	Urinary Hesitancy		52.9	43.1	37.9	60.5	66.7	45.3
	Urinary Retention		5.9	24.1	12.6	36.8	33.3	20.0
	Urinary Incontinence		17.6	31.0	18.4	44.7	66.7	28.0
	Bowel Dysfunction		29.4	39.7	32.0	50.0	44.4	37.3
Cognitive	Depression		17.6	12.9	11.7	26.7	11.1	14.0
	Euphoria		2.9	3.6	1.9	5.3	11.1	3.33
	Decreased mentation		17.6	17.2	15.5	21.1	22.2	17.3

Table 2-5: Factors affecting presence of clinical signs in study cohort

System	Clinical sign	Site	Clinical factor									
			Male sex		Age (years)		Disease duration (m)		RRMS		PPMS	
			p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR
Pyramidal	Increased tone	Arm	0.001	8.54	0.116		0.274		<0.001	0.068	0.818	
		Leg	0.435		0.470		0.309		<0.001	0.273	0.222	
	Weakness	SA	0.205		0.485		0.519		0.034	0.293	0.969	
		EF	0.018	3.87	0.297		0.988		0.053		0.824	
		EE	0.017	4.57	0.482		0.572		0.039	0.240	0.346	
		HF	0.518		0.049	1.036	0.013	1.005	<0.001	0.292	0.332	
		KF	0.463		0.776		0.166		<0.001	0.309	0.069	
		KE	0.015	2.77	0.159		0.961		0.001	0.262	0.123	
		ADF	0.151		0.317		0.546		<0.001	0.170	0.332	
		APF	0.223		0.325		0.503		<0.001	0.169	0.053	
	Brisk Reflexes	Bicep	0.319		0.215		0.045	1.004	0.924		0.333	
		Supina-tor	0.048	2.29	0.459		0.043	1.005	0.209		0.458	
		Tricep	0.488		0.105		0.032	1.005	0.569		0.262	
		Knee	0.215		0.112		0.633		0.019	0.472	0.860	
		Ankle	0.008	2.79	0.062		0.163		0.678		0.311	
	Extensor plantar	Plantar	0.127		0.413		0.112		<0.001	0.117	0.216	
Sensory	Reduced superficial sensation	Arm	0.047	1.80	0.360		0.515		<0.001	0.327	0.166	
		Leg	0.292		0.798		0.195	0.001	0.403		0.009	0.162
	Reduced vibration	Arm	0.173		0.157		<0.001	1.008	0.002	0.297	0.996	
		Leg	0.190		0.296		<0.001	1.022	0.996		1.000	
	Reduced proprioceptio n	Arm	0.526		0.122		0.008	1.01	0.008	0.177	0.998	
		Leg	0.282		0.346		0.640		<0.001	0.133	0.071	
	Rhombergs +		0.765		0.319		0.650		<0.001	0.085	0.331	
Cerebellar	Dysmetria	Arm	0.252		0.500		0.028	1.005	0.302		0.305	
		Leg	0.808		0.832		0.067		<0.001	0.218	0.545	
	Dysdiadocho k.	Arm	0.153		0.572		0.007	1.006	0.011	0.338	0.127	
		Leg	0.302		0.287		0.155		<0.001	0.210	0.216	
	Gait	Eye open	0.529		0.409		0.074		<0.001	0.043	0.999	
		Eye close	0.752		0.419		0.073		0.006	0.120	0.999	
Visual	Optic Atrophy	Eye	0.354		0.360		<0.001	1.007	0.022	0.507	0.050	0.205
	Acuity >6/6		0.056		0.877		0.003	1.005	0.005	0.257	0.387	
	Scotoma		0.004	0.33	0.431		0.008	1.006	0.021	0.419	0.237	
Brainstem	Nystagmus		0.020	3.11	0.593		0.113		0.096		0.374	
	Dysarthria		0.782		0.231		0.683		0.036	0.361	0.963	
	Dysphagia		0.489		0.594		0.530		0.009	0.201	0.104	
Sphincter	Urinary Hesitancy		0.120		0.971		0.025	1.006	0.060		0.557	
	Urinary Incontinence		0.296		0.151		0.121		0.028	0.376	0.230	
	Urinary retention		0.047	0.21	0.075		0.839		0.012	0.303	0.608	

(3) Results summary

Table 2-6: Summary of clinical signs found to be significantly affected by patients sex (statistically significant at 0.05 level and corrected for age, disease duration and disease sub-type).

Clinical sign	p-value	OR for male sex (95% CI)
Arm Tone Raised	0.001	8.543 (2.547 – 28.650)
Weakness Elbow Flexion	0.018	3.868 (1.267 – 11.810)
Weakness Elbow Extension	0.017	4.571 (1.313 – 15.915)
Weakness Knee Extension	0.015	2.77 (1.217 – 6.305)
Brisk Supinator Reflex	0.048	2.293 (1.008 – 5.217)
Brisk Ankle Reflex	0.008	2.789 (1.306 – 5.955)
Presence of Nystagmus	0.020	3.111 (1.200 – 8.064)
Impaired LT/PP sensation in upper limbs	0.047	1.800 (1.009 – 3.210)
Presence of Visual Scotoma	0.004	0.329 (0.154 – 0.700)
Presence of Urinary Retention	0.047	0.213 (0.046 – 0.982)

Table 2-7: Summary of signs more likely to be found with increasing disease duration (statistically significant at 0.05 level and corrected for age, sex, and disease subtype).

Sign	p-value	Odds Ratio (95%CI) (monthly)	Years to double odds
Weakness of hip flexion	0.013	1.005 (1.001 -1.008)	12
Brisk Bicep Reflex	0.045	1.004 (1.000 – 1.009)	15
Brisk Supinator Reflex	0.043	1.005 (1.000 – 1.009)	12
Brisk Tricep Reflex	0.032	1.005 (1.000 – 1.010)	12
Finger Nose ataxia	0.028	1.005 (1.001 – 1.009)	12
Dysdiadochokinesis (upper limbs)	0.007	1.006 (1.002 – 1.011)	10
Decreased Vibratory Sensation (upper limbs)	<0.001	1.008 (1.004 – 1.013)	8
Decreased Vibratory Sensation (lower limbs)	<0.001	1.022 (1.011 – 1.033)	3
Decreased Proprioception (upper limbs)	0.008	1.010 (1.003 – 1.117)	6
Urinary Hesitancy	0.025	1.006 (1.001 – 1.011)	10
Impaired Visual Acuity	0.003	1.005 (1.002 – 1.009)	12
Optic Atrophy	<0.001	1.007 (1.004 – 1.011)	9
Visual Scotoma	0.008	1.006 (1.001 – 1.010)	10

Table 2-8: Summary of signs less likely to be found in relapsing remitting disease compared with secondary progressive disease (statistically significant at 0.05 level and corrected for age, sex, and disease duration).

Sign	p-value	Odds Ratio (95%CI)
Arm Tone Raised	<0.001	0.068 (0.017 – 0.268)
Leg Tone Raised	<0.001	0.273 (0.150 – 0.499)
Weakness of Shoulder Abduction	0.034	0.293 (0.094 – 0.912)
Weakness of Elbow Extension	0.039	0.240 (0.062 – 0.928)
Weakness of Hip Flexion	<0.001	0.292 (0.161 – 0.530)
Weakness of Knee Flexion	<0.001	0.309 (0.171 – 0.557)
Weakness of Knee Extension	0.001	0.262 (0.115 – 0.598)
Weakness of Ankle Dorsi-Flexion	<0.001	0.170 (0.073 – 0.397)
Weakness of Ankle Plantar-Flexion	<0.001	0.169 (0.082 – 0.349)
Brisk Knee Reflex	0.019	0.471 (0.251 – 0.882)
Extensor Plantar Reflex	<0.001	0.117 (0.63 – 0.219)
Heel-Shin Ataxia	<0.001	0.218 (0.76 – 0.631)
Dysdiadochokinesis (upper limbs)	0.011	0.338 (0.146 – 0.781)
Abnormal RAM (lower limbs)	<0.001	0.210 (0.114 – 0.387)
Gait Ataxia (Eyes open)	<0.001	0.043 (0.010 – 0.193)
Gait Ataxia (Eyes closed)	0.006	0.120 (0.27 – 0.541)
Dysarthria	0.036	0.361 (0.139 – 0.937)
Dysphagia	0.009	0.201 (0.060 – 0.672)
Decreased LT/PP Sensation (upper limbs)	<0.001	0.327 (0.186 – 0.576)
Decreased LT/PP Sensation (lower limbs)	0.001	0.403 (0.231 – 0.703)
Decreased Vibratory Sensation (upper limbs)	0.002	0.297 (0.136 – 0.650)
Decreased Proprioception (upper limbs)	0.008	0.177 (0.049 – 0.642)
Decreased Proprioception (lower limbs)	<0.001	0.133 (0.056 – 0.315)
Positive Rhombergs test	<0.001	0.085 (0.031 – 0.235)
Urinary Incontinence	0.028	0.376 (0.158 – 0.897)
Urinary Retention	0.012	0.303 (0.119 – 0.771)
Impaired Visual Acuity	0.005	0.257 (0.088 – 0.752)
Optic Atrophy	0.022	0.507 (0.283 – 0.907)
Visual Scotoma	0.021	0.419 (0.200 – 0.879)

Table 2-9: Summary of signs less frequently found in primary progressive disease compared with secondary progressive disease (statistically significant at 0.05 level and corrected for age, sex, and disease duration).

Sign	p-value	Odds Ratio (95%CI)
Decreased LT/PP Sensation (lower limbs)	0.009	0.162 (0.042 – 0.629)
Optic Atrophy	0.050	0.205 (0.042 – 0.997)

Discussion

We have reported the incidence of a comprehensive set of varying clinical signs in 150 patients with multiple sclerosis and shown how they vary within the group according to patient sex, age, disease duration and disease subtype. We have statistically analysed this data and shown that whilst the majority of clinical signs are more likely to be evident in patients with secondary progressive disease, there are also clinical signs that seem more likely to appear in relation to overall disease duration. We have also revealed that certain clinical signs are more frequently found in relation to the patient's sex but rarely is age at assessment independently associated with the presence of clinical signs.

Our cohort is unlikely to be truly representative of our geographical multiple sclerosis population. Our data has been collected from a clinic designed to assess the suitability of multiple sclerosis patients for disease modifying drugs[31;32;123;124] and whilst the only referral criteria was a secure diagnosis of multiple sclerosis according to the McDonald criteria[15], most referrers were aware that patients with relapses and without marked disability were more likely to be suitable. Hence our cohort probably shows more relapsing disease and less severe disability than would be expected by chance in a truly unselected prevalent population.

Previous studies[17;122;125;126] of clinical multiple sclerosis are rarely unaffected by inherent selection bias, usually due to the hospital based nature of recruitment. Other differences between studies include the diagnostic criteria used[13;15]; varying geographical and racial distributions[125]; and the obvious but salient fact that clinical signs are observer dependent. Therefore comparison with previous studies is therefore only partial instructive. We have however provided the details of 2 previous studies, both performed within mainland Britain in table format for comparison[7;122] (see table 2-3). It should be borne in mind that our reported frequencies pertain to individual clinical signs rather than a cumulative chance within a patient, thus a figure of 54% for weak hip flexion in secondary progressive patients (see table 2-4) indicates that 54% of all hips were weak in this sub-group and as each patient has 2 hips the chances of any hip weakness within an individual will be somewhat higher.

Initial analysis of our cohort's demographic data reveals a higher proportion of females as widely reported in other series (see table 2-1 and figure 2-1). Whilst we did observe an unexpected preponderance of females in our primary progressive group, our group size is clearly not sufficient to challenge the conventional belief that there is probably sexual equality amongst primary progressive patients.

Our cohort's age of onset is comparable with previous studies (see table 2-1 and figure 2-2). Our combined cohorts mean age of onset of 30.6 years is very similar to previous larger studies which have reported figures of 31.3 years[121] and 30.5 years[17]. Our average age of onset of relapsing remitting disease and secondary progressive disease are similar as one would expect of disease subtypes that are largely the same disease at different stages of evolution. The important caveat to this is that there is a small group of relapsing-remitting patients who will never enter the secondary progressive phase and so it is not unreasonable that there is a small difference between these groups. The age of onset (40.67 years) in our primary progressive patients was substantially later than in relapsing onset disease and was comparable with previous studies [127-129].

We did not record the date of onset of progressive symptoms. Previous observations[129] indicate that the progressive phase starts at a remarkably similar age in both secondary and primary progressive patients.

Our disease duration statistics (see table 2-1) show that on the whole our patients are at a relatively early stage of their disease. This is in keeping with the nature of the disease-modifying clinic to which they were referred. This would also explain the relatively low proportions of patients from a prevalence perspective of progressive disease sub types.

Our disability data, as measured by the EDSS[19] (see figure 2-3 and table 2-2) varies from previous cross sectional analyses as we have relatively fewer patients with advanced EDSS scores[17]. This is again presumably a result of the previously noted referral bias towards less disabled patients.

Notably we had no patients at EDSS zero. This was consistent with the cross-sectional disabilities reported in a much larger previous study[17] of 1099 patients. It does seem difficult to reconcile the traditional view of relapsing-remitting disease where clinical signs are 'not infrequently absent'[117]. with the notion that not one of the 1249 patients in either of our studies was normal to neurological examination. *Therefore one of the following is probably true: remission after 2 disease-defining relapses is virtually never complete or there is a parallel insidious progression of neurological deterioration (albeit less disabling than in classical progressive disease) that commences following, or even preceding the first or second relapse*[23]. Recent studies suggest atrophy and axonal loss are present very early in the course of multiple sclerosis[38;130-132]. The magnitude of this atrophy is such that it may have been evident, if looked for, before the first clinical episode of acute neurological deterioration[51]. There is also neuro-physiological evidence of early asymptomatic visual disturbance that supports this hypothesis[133]. Indeed a recent therapeutic study[134] of clinically isolated demyelination found their 91 patients to have a mean EDSS of 2.2 at entry to their study. It may therefore be the case that a proportion of patients are already at EDSS 1.0 or higher in advance of developing symptoms.

Our primary progressive group has a very similar temporal disability course to previous studies. The London, Ontario cohort and Lyon cohort of primary progressive patients were found to take 8 years[23] and 7.1 years[10] respectively to reach an EDSS of 6. Our primary progressive group, albeit much smaller, had a median EDSS of 6 (mean 5.83) at a disease duration of 7.89 years.

Our findings that primary progressive patients had a similar EDSS distribution to secondary progressive patients despite a much shorter disease duration parallels previous observations[10] that disability evolves substantially more rapidly in progressive rather than relapsing onset disease.

Therefore whilst our group demonstrates a modest bias towards earlier relapsing disease than would be expected from a truly unselected multiple sclerosis population we believe that the differences between our sub-groups in terms of sex, age, disease duration and disease subtype are not incomparable with previous studies.

(i) Visual Signs

We found corrected visual acuity to be worse than 6/6 on Snellen chart testing in 25.7% of all our patient's eyes (see Table 2-4). This is lower than a previous series of 301 patients studied by Dr Swingler[7] (see Table 2-3) in a similar geographical location, who reported impaired visual acuity in 72.4% of these patients. This is probably due to the differences in reporting the proportion of eyes versus patients and also as previously mentioned the bias in our population towards earlier disease states. This is given further credence by our finding that impaired visual acuity was statistically significantly (p=0.003) more likely with increasing disease duration. Assuming our Odds Ratio correct this would equate to a doubling of risk of impaired visual acuity every 12 years of disease duration (see table 2-7).

Optic atrophy as defined by optic disc pallor was found in 32% of *eyes* in our cohort. This is probably comparable to the 41% of *patients* with optic atrophy reported by Dr Swingler (see Table 2-3). Factors that appeared to affect the presence of optic atrophy (see Table 2-5) were increasing disease duration (p<0.001) and both relapsing remitting (p=0.022) and primary progressive disease (p=0.05) appeared to have significantly lower incidences of optic atrophy compared with secondary progressive disease. Visual field abnormalities to confrontational testing were uncommon in our group.

Visual scotoma was found in 10.7% of our patients eyes over all. It appeared more likely to be found with increasing disease duration (p=0.008) and less likely to be found in relapsing remitting disease (p=0.021) and, inexplicably, men (p=0.004).

Previous work[135] has suggested that episodes of optic neuritis *per se* infrequently result in impaired visual acuity in the long term, this study also found that visual acuity was more likely to be impaired in optic neuritis patients with multiple sclerosis than those without MS. This suggests that visual impairment in multiple sclerosis is not dependent upon episodes of optic neuritis. A supporting observation from our group was that primary progressive patients, who had no episodes of optic neuritis, were found to have the highest incidence of impaired visual acuity but the lowest incidence of observed optic atrophy. The lower incidence of optic atrophy in

primary progressive patients was statistically significant compared to secondary progressive patients (p=0.05). Impaired visual acuity was more common in primary progressive patients than relapsing onset disease, although this did not reach statistical significance. However the casual observation of impaired visual acuity in a group with paradoxically low levels of optic atrophy is interesting. It possibly suggests that dysfunctional axons and myelin are relatively preserved in primary progressive disease compared with secondary progressive disease, preventing optic atrophy. However the functional paradigm is that visual acuity in primary progressive patients may be worse. Inflammatory or apoptotic 'pruning' of dysfunctional neurological tissue may lead to a paradoxically better functional outcome.

(ii) Pyramidal signs

Our study (see table 2-4) confirmed the received wisdom that increased tone in multiple sclerosis is more frequent in lower than upper limbs and is more likely in progressive disease than relapsing remitting disease. We also found that raised arm tone appeared to be significantly (p=0.001) more likely in males (see table 2-5). This trend towards more marked pyramidal signs of disease in males, is not produced from a skew towards primary progressive disease or late onset disease as this was not found in our cohort. Neither could disease duration explain this as our male patients had a shorter disease duration (table 2-1).

Interestingly disease duration was not independently associated with raised limb tone. Our models indicate that the presence of progressive disease was the major determinant in the presence of raised limb tone.

Clinically detectable limb weakness is more common in legs than arms in our study (see table 2-4). Hip flexion was the movement most commonly weak. A 'pyramidal' pattern of leg weakness was observed with weakness of knee flexion substantially more common than weakness of knee extension (28.3% vs. 12.3%). A pattern of 'pyramidal' arm weakness (elbow flexion stronger than elbow extension) was not observed except in our primary progressive group.

Men were significantly more likely to have weakness of elbow flexion, elbow extension and knee extension (see table 2-5) than females. This in combination with the above observations of significantly increased frequency of raised arm tone in males has supporting evidence from a pathological study[136] that found that nerve fibre density in the crossed pyramidal tracts at the C3 spinal level was significantly reduced in males compared with females (41% male vs 19% female reduction, $P<0.003$). This reduction in nerve fibre density was unrelated to local plaque formation. There was no difference between the sexes in healthy controls in this study. Whilst weak hip flexion alone was significantly more common with increasing disease duration the notable trend was towards limb weakness being significantly more likely in progressive rather than relapsing remitting disease, and being otherwise independent of disease duration.

We were surprised initially to find such a low incidence of brisk reflexes in our cohort (see table 2-4) compared to previous studies which quote figures of 92.8%[122] and 59.1% (see table 2-3) for hyper-reflexia. This is probably due to a combination of factors. We are examining and reporting individual reflexes as opposed to noting the presence of any hyper-reflexia as well as our cohort's tendency towards earlier relapsing disease. However the persistent variance between these three reported incidences of hyper-reflexia may also emphasise the limitations of subjective examinations and highlight that comparing between centres and observers is of limited value.

In contrast, relative observations made by the same observers at the same centre are, we believe, perhaps more instructive. Brisk ankle and radial reflexes were more common in men. Arm reflexes showed a statistical trend towards being brisk with increasing disease duration whereas knee reflexes were more likely to be brisk in progressive rather than relapsing remitting disease without an independent effect of disease duration. We also found that reflexes were not infrequently absent. Reflexes were not found in 6.7% of knee reflexes and 12.3% of ankle reflexes. This parallels earlier findings of reflex absence in 13% of MS patients[137].

Overall 41% of plantar reflexes were extensor on examination although there were marked variations depending on whether the patient was in the relapsing remitting

(24.3%), secondary progressive (75%) or primary progressive (88.9%) disease phase. This provides partial support for the hypothesis that an extensor plantar may be a useful sign of impending secondary progression[138]. There was no independent effect of disease duration on presence of extensor plantar reflexes.

(iii) Cerebellar signs

Ataxia refers to disturbance in the smooth performance of voluntary motor acts[139]. It encompasses dysmetria, dysdiadochokinesis and past pointing. The tremor found in multiple sclerosis, although complex, is considered to be largely cerebellar in origin[140]. Our analysis of cerebellar signs reveals a higher incidence of ataxia in legs than arms (see table 2-4). This contrasts with previous studies[113;122], however at least one of these studies[122] notes that their excess of cerebellar signs in the upper limbs 'is explained by the frequent presence of a marked spastic paraparesis precluding the testing of cerebellar function in the lower limbs. When it can be tested, cerebellar dysfunction is more common in the lower limbs'[141]. The trend towards less severe disability levels in this study may again offer partial explanation for this but it is accepted that despite best efforts confidently distinguishing cerebellar ataxia from a pseudo-pyramidal ataxia is rarely easy. Our two measures of ataxia – essentially dysmetria and dysdiadochokinesis – disclosed very similar information. Dysmetria and past pointing in the arms was significantly ($p=0.028$) more likely with increasing disease duration (see table 2-5) but we did not find an independent correlation with disease subtype. Dysdiadochokinesis in the arms was independently correlated with disease duration ($p=0.007$) and secondary progressive disease ($p=0.011$). In the legs both dysmetria and dydiadochokinesis were significantly ($p<0.001$) less likely in relapsing remitting disease. We did not find a statistically significant independent effect of disease duration on leg ataxia.

We found resting tremor in only 3% of arms and 0.7% of legs. This is similar to the findings of a study of tremor in 100 patients with multiple sclerosis[140] (mean disease duration 18.8 years) which found no examples of rest tremor. They did, however, find postural or kinetic tremor in 58 of their patients. Our very low incidence of rest tremor further highlights the fact that basal ganglia function is usually preserved in multiple sclerosis.

Gait, although reported as part of the cerebellar examination is clearly reliant on several neurological systems including pyramidal, visual, brainstem and sensory. This is highlighted by the worsening of gait with eye closure. However abnormalities of gait with the eyes open better distinguished relapsing from progressive disease ($p<0.001$) whilst gait abnormalities with eyes closed are frequent even in relapsing remitting disease and may be a sensitive early marker for multiple sclerosis, possibly of use in stratifying risk of developing multiple sclerosis from clinically isolated syndromes. Longer disease duration was not found to be an independently significant ($p=0.074$) cause of gait impairment.

(iv) Brainstem signs

The analysis of brainstem signs, principally inferred through the examination of cranial nerves, is shown in table 2-4. Our overall figure of 10.7% of patients with eye movement abnormalities is comparable with the 13% of patients found to have diplopia on examination in a previous study[126] of 991 patients. Our figures for individual signs are generally less than in previous studies (see table 2-3) although similar ratios between the various signs are observed. As previously mentioned this is likely to be a reflection on our group's bias towards earlier disease.

We found nystagmus appeared to be more common in men ($p=0.020$), whilst dysarthria ($p=0.036$) and dysphagia ($p=0.009$) appeared to be significantly more common in secondary progressive rather than relapsing remitting disease. Disease duration did not independently appear to affect the likelihood of finding these signs.

(v) Sensory signs

We found that vibratory sensation was most frequently abnormal whereas proprioception was most likely to be preserved. Sensation to touch and pain was somewhere between these two extremes (see table 2-4).

In considering our findings for touch and pain sensation it is important to consider the protocol by which our examinations and assessments were performed (see

Appendix X). Superficial sensation is assessed by both light touch and pin prick sensation. Whilst with hindsight it would have been useful to discriminate between light touch and pinprick sensation as they are generally carried in different pathways it is our recollection that a large majority of abnormal results were associated with abnormal pinprick sensation whereas an isolated abnormality of light touch sensation was very unusual. For this reason we believe that our findings in this category of superficial sensation principally reflect dysfunction in the spino-thalamic tracts of the spinal cord.

Of note we did not find a dramatic difference in the loss of normal superficial sensation between arms and legs. If sensory loss occurs secondary to focal demyelination and chronic plaque formation one would expect leg sensation to be significantly worse than arm sensation due to the greater length of central nervous system white matter that the leg sensory neurons have to traverse compared with the arms. This was not the case, and seems to be counter-intuitive at first site. A previous study[142] of pain evoked sensory potentials found that of twelve patients, three had delayed sensory evoked potentials in the hands, whilst seven had delays in the feet. In our experience clear sensory levels are difficult to find in patients with multiple sclerosis. We found this to be the case even when we were forearmed with knowledge of clear and focal abnormalities of spinal MRI in 10 of our patients. This would concur with a recent study that found axonal injury in the spinal cord occurs largely independently of T_2 lesions[143]. Another study of axonal loss in multiple sclerosis found a statistically significant loss of axons in the sensory tracts of the spinal cord only in the upper and lower segments of the cervical cord. The axonal loss was most marked in the upper cervical cord. These findings would tend to suggest that there is likely to be little difference in sensation between upper and lower limbs. At the point where the sensory tracts reach the lower cervical cord the majority of the damage has been done. Even axons lost in the lower cervical cord (C5-8) will probably affect sensory disturbance in the arms, to a degree, in addition to the legs. There may in fact be a sensory level between occiput (C2) and vertex of the skull but this is not routinely examined for. This similarity between sensory disturbance in arms and legs is despite data in the next chapter that reveals relapses affecting sensation in the legs are more commonly reported than in the arms. Certainly acute relapses do seem to more commonly affect sensation in the legs.

possibly with a clear sensory level at the time of the relapse. However this, in our experience, does not frequently translate into a chronic sensory level.

Factors that appeared to increase the presence of abnormal superficial sensation were being in a secondary progressive stage of the disease compared to relapsing remitting for both arms ($p<0.001$) and legs ($p=0.001$). Also we noted a tentative relationship between male sex ($p=0.047$) and increased incidence of superficial sensory abnormalities in the arms.

Perhaps most strikingly primary progressive patients were found to have a significantly ($p=0.009$) lower incidence of superficial sensory abnormalities in their legs compared to secondary progressive patients. In our cohort the incidence of superficial sensory abnormalities in the legs of primary progressive patients was lower than in their arms or in the legs of even relapsing remitting patients. Despite being statistically significant at 0.01 level we were concerned that this may be a false positive result and so again checked our original forms to ensure correct data entry and examined our qualitative data. This showed the same trend. It does however seem unlikely that such a finding would have evaded prior detection by other investigators and a rational explanation is not obvious, raising the possibility that this is a false-positive result but for two reasons we believe this finding at least merits further investigation. Firstly it is of note that this quite marked finding was not suspected by ourselves even after the data collection phase, only upon systematic analysis of our data did it become obvious that there was a marked difference between two groups in whom we had not anticipated a significant difference. This raises the possibility that significant differences and intricacies in multiple sclerosis may be beyond experiential detection. We also checked our qualitative data, which showed the same trend. If we compare only the legs of the two progressive groups who have an abnormality of superficial sensation then we see that of the 3 affected legs in the primary progressive group all have only a mild abnormality. This compares with 13 mild, 20 moderate and 11 marked abnormalities in the secondary progressive group. Clearly this result could still be obtained by chance, especially when so many observations have been made and a rationale explanation for this finding is not obvious. If this finding were prospectively validated in a new cohort

then it may help further our understanding of the differences between the progressive disease forms.

Vibratory sensation was found to be abnormal in 87.3% of all legs. This corresponds with anecdotal observations[144] but is somewhat greater than previous studies which have reported impaired vibratory sensation in 61.5% (see Table 2-3) and 62.5%[122] of patients. Impaired vibratory sensation seemed to be most affected by disease duration ($p<0.001$) rather than whether the patient was in a progressive disease phase. None of four patients with a disease duration of 12 months or less had any impaired vibratory sensation whilst only one of sixty six patients with a disease duration over 92 months was similarly unaffected. Vibratory sensation may have some potential as an early surrogate marker for disease progression in therapeutic trials aiming to show early preservation of neurological function.

We found proprioceptive abnormalities to be uncommon in our cohort and principally worse in legs than arms (see table 2-4). In upper limbs proprioceptive abnormalities became more likely (see table 2-5) with increasing disease duration ($p=0.008$) and in secondary progressive disease ($p=0.008$) rather then relapsing remitting disease whereas in lower limbs only the presence of secondary progressive disease was independently associated with an increased incidence of proprioceptive abnormalities.

Romberg's test, although principally a test of proprioception clearly relies on other sensory and motor modalities. This is highlighted by the fact that many more of our patients had a positive Rombergs (would have fallen if not caught) than individual abnormalities of proprioception. Rombergs was more likely to be positive if the patient was in a progressive disease stage (<0.001) but disease duration was not found to be independently significant to Romberg's test.

(vi) Bladder and bowel symptoms

Sphincter dysfunction was assessed from the patient's history rather than examination. In our group (see table 2-4) we found urinary urgency (57.3%) to be the

most common symptom followed by urinary hesitancy (45.3%), bowel dysfunction (37.3%), urinary incontinence (28.0%) and urinary retention (20%). These figures are somewhat higher than previous studies who have similarly reported these as separate entities[122] (see Table 2-3), but overall likely similar to previous studies who have reported sphincter disturbance as a single entity. One study[125] found sphincter disturbance in 74% of patients with multiple sclerosis in a similar geographical location.

Analysing factors that possibly affect the onset of sphincter disturbance we found that urinary hesitancy was more often found with advancing disease duration ($p=0.025$), but not independently associated with disease sub-type (see table 2-5). Urinary incontinence and urinary retention were both more commonly found in secondary progressive disease rather relapsing remitting disease but neither symptom was found to be independently affected by disease duration.

(vii) Mood and cognitive symptoms

Analysis of mood and intellectual function (see table 2-4) revealed that our patients were more likely to be depressed (14%) than euphoric (3.3%), in contrast to a Scottish series[122] which reported euphoria in 17.4% and depression in only 7.5%. Our patients more frequently reported new cognitive and memory problems (17.3%) compared with their Scottish counterparts[122] (6.1%), but about as frequently as patients from Wales[113] (13.3%).

We found no statistically significant effects of patient sex, age, disease duration or disease subtype on the development of these symptoms.

Factors affecting the neurological examination:

(i) Age

The age of the patients at the time of clinical examination did not appear to independently affect the clinical examination. Only weakness of hip flexion achieved an independent 'statistical' trend ($p=0.049$), with increased incidence of weakness

with increasing age. However the marginal nature of this result in the context of the number of possible associations examined should limit the conclusions drawn from this result. Although ours, and previous studies[122] have found progressive onset disease more likely to have a later age of onset, we did not find that age independently affected the presence or absence of signs except for hip flexion mentioned above. This indicates that advancing age is probably not a significant independent determinant of the presence of clinical signs, and ultimately disability in multiple sclerosis. Any observation of more advanced disability in the aged patients of a cross sectional population is probably due to a combination of longer disease duration and higher probability that the disease was progressive from onset rather than aging per se. In conclusion the neurodegenerative abilities of natural aging is trivial compared to the effects of multiple sclerosis. Our findings are somewhat different to those of Confavreux who found in the large Lyon cohort that the age at which certain stages of disability were achieved was very similar whether the disease onset was relapsing or progressive, thus making age a key determinant in disability[120] and further suggesting that relapses are largely inconsequential in the long term formation of disability. It may be that within our cohort the relatively small number of primary progressive patients, consequent upon the clinic setting, and the co-analysis of disease duration, has down played the role of ageing.

(ii) Sex

Male sex was associated with an increasing incidence of several signs (see table 2-6). Increased arm tone; weakness of biceps, triceps and quadriceps; brisk ankle and radial reflexes; impaired superficial sensation in the arms and nystagmus were all significantly more common in men in our study. When the various signs are considered together, there does appear to be a trend towards pyramidal tract signs in men. This is independent of age, disease duration and presence of primary progressive disease.

Gender is undoubtedly important in multiple sclerosis[145]. Multiple sclerosis is less common in males. It is known that males with multiple sclerosis generally have a more progressive and severe outcome than females [6;22]. Gender may affect not only alter the susceptibility of the central nervous system to damage but also its intrinsic

repair mechanisms[146-148]. MRI studies in multiple sclerosis have found that whilst males have relatively fewer inflammatory central nervous system lesions, paradoxically they tend to have more destructive lesions than females[149,150].

The pathophysiological basis for this effect of gender on phenotype is not entirely clear. It is certainly not a phenomenon limited to multiple sclerosis but is evident in many inflammatory diseases including systemic lupus erythematosis and rheumatoid arthritis[151]. Gender differences in multiple sclerosis could be a direct effect of the Y chromosome (or lack of the second X chromosome), an indirect effect mediated by sex hormones or a gender specific environmental effect. Several observations suggest that of these different factors sex hormones are most likely to be relevant to multiple sclerosis.

Clinical observations of multiple sclerosis suggest clear changes in disease activity with alterations in sex hormone production in females. Pregnancy has long been associated with a reduction in relapse rates and first ever episode of multiple sclerosis, especially during the third trimester[145]when compared with non-pregnant states. The post partum period seems to be associated with a compensatory increase in disease activity. Pregnancy is also associated with an improvement in other auto-immune diseases such as rheumatoid arthritis[152]. The reasons for this are thought to be an evolutionary suppression of Th1-type immune responses that can cause fetal rejection. Both oestrogen and progesterone levels gradually increase during pregnancy. Treatment of animal models of multiple sclerosis and rheumatoid arthritis suggest that oestrogen rather than progesterone is responsible for the beneficial immunomodulation[145].

Testosterone appears to be protective in a variety of auto-immune diseases[153] perhaps explaining the lower incidence of multiple sclerosis in men. The later onset of multiple sclerosis in men may be explained by the decline in bio-available testosterone observed in middle aged men[154]. It is suggested therefore that young men may be protected from multiple sclerosis by high testosterone levels.

One study[155] of 60 patients with relapsing-remitting multiple sclerosis investigated the relationship between serum sex hormone concentrations and characteristics of

tissue damage on conventional MRI brain scans in men and women suffering from relapsing-remitting MS. In women it was found that serum testosterone was significantly lower in MS patients than controls (p=0.0001) and that the lowest levels of testosterone were found in females with the greatest number of gadolinium enhancing lesions (p=0.02). Higher serum testosterone levels in females were associated with a significantly greater T_1 lesion load (p=0.006). Oestradiol concentrations did not significantly affect the MRI appearances in women. However, in males it appeared that oestradiol and not testosterone was affecting MRI brain appearances. In males a positive correlation was found between oestradiol concentrations and both T2 (p=0.02) and T1 (p=0.04) lesion load whereas testosterone levels were not associated with MRI parameters. The above study indicates that sex hormones play a role in the development of MRI lesions, although further work is required to examine this phenomenon in more detal, particularly whether spinal cord lesions are similarly affected.

Whilst several previous studies[156-159] have found male sex is associated with a more rapid accumulation of composite disability the nature of this disability is not made clear. A large study of primary progressive patients found that there was similar disability progression between the sexes in the early stages of the disease but that survival in males was significantly shorter than in females[5]. Our data shows a trend towards spasticity, weakness and hyper-reflexia particularly in the upper limbs of men. The relatively poor outcome for cortico-spinal tracts in males has previously been noted in pathological studies[136]. That this finding in our study is independent of the presence of primary progressive disease suggests that men are generally more susceptible to a cortico-spinal pattern of disease that is not dependent upon their propensity for primary progressive disease. It has previously been observed[7] that the gender differences in multiple sclerosis is likely due to females having a relatively pro-inflammatory phenotype compared with males. However this does not immediately explain why men are not found at the less severe end of the disease spectrum. In spite of their inherently 'anti-inflammatory' sex, men appear to selectively suffer more severe damage to some of the most functionally useful neurological pathways. This may be because some inflammation in a multiple sclerosis population is beneficial[26;160-162] and a males relative lack of inflammation can thus be plausibly associated with a more disabling disease phenotype.

(iii) Disease duration and disease sub-type

Intuitively multiple sclerosis should get worse the longer you have it and we already know that primary and secondary progressive disease are associated with more advanced disability when compared to relapsing remitting disease[10]. However the disease duration and disease sub-type are partially correlated. The longer the disease duration the more likely secondary progressive disease is to have commenced. But which is the more important factor with regard to the development of clinical signs?

Our results indicate that many clinical signs within a population of multiple sclerosis become apparent depending on whether secondary progression has occurred, without independent regard for the disease duration (see table 2-8). Less frequently signs (eg leg vibratory sensation, brisk arm reflexes) appear more commonly with advancing disease duration (see table 2-7), without apparent independent regard for secondary progression. Vibration sensation, particularly in the legs seems to become uniformly impaired at a stage well in advance of recognised secondary progression – raising the possibility that the secondary progressive stage may be dispersed in time and consequent upon properties of the underlying pathway: degree of myelination, axonal size, proximity to cerebrospinal fluid, functional reserve and plastic capabilities. Formal diagnosis of secondary progression may only occur at the stage at which the cortico-spinal tracts enter this phase.

Often both disease duration and secondary progression were risk factors for presence of clinical signs independent of each other. Overall a clear majority of signs that might be expected to have a greater impact on mobility and thus disability scales (i.e. EDSS) such as leg weakness, were found to be independently associated with presence of disease progression rather than disease duration. This echoes the findings of previous longitudinal natural history studies that report the presence of progressive disease to be the most ominous prognostic feature[10;11].

Whilst a highly variable clinical phenotype between individuals with multiple sclerosis is self evident, our findings suggest that not all neurological pathways within a population of patients with multiple sclerosis degenerate in identical ways.

Some clinical signs seem to appear in a constant time dependent manner whilst the majority seem more prone to a step-wise deterioration heralded by the onset of secondary progression. Due to plasticity and luxury function it may be that constant rates of axon loss result in apparent stepwise neurological dysfunction at a time remote from the onset of pathology. Our findings that leg weakness is highly correlated with the secondary progressive phase may indicate that axonal loss is relatively constant with the cortico-spinal tracts reaching the limit of their functional reserve and thus defining the point at which clear progression of disability is observed. Alternatively there may be a distinct pathological process that occurs at the time of disease progression that is independent, although possibly co-incidentally related, to the onset of relapsing disease

The recent work of DeLuca et al[119] examining axonal loss in the spinal cord found axonal loss varied dependent upon tract type and segment of the cord. Sensory tract axonal loss was only statistically significant compared with controls in the upper cord, whilst corticospinal tract loss was significant at all levels. Further examination of the corticospinal tracts and the upper cervical sensory tracts revealed that there was selective preservation of large (>3μm) diameter fibres. This provides histopathological evidence that axonal loss is site and size dependent. Although the precise function of small and large fibres are yet to be fully elucidated it may be that the variance in clinical signs according to disease duration and disease sub-type that we have observed are also as a result of varying site and size specific axonal loss.

Whilst in mild contrast to our study DeLuca et al[119] found few correlations with disease duration and histopathology it should be remembered that post-mortem studies may not pick up dynamic changes occurring at lower disability levels.

(iv) Differences between primary and secondary progressive multiple sclerosis?

Of further interest was our comparison of clinical signs in secondary progressive and primary progressive disease. Although neglected for some time there is renewed interest in primary progressive disease[163]. Overall clinical examination reveals many more similarities than differences between primary and secondary progressive MS (see table 2-5 and 2-9). However our finding of preservation of superficial sensation

in the lower limbs of primary progressive patients (p=0.009) compared with secondary progressive patients was striking and merits further study. The finding of relatively low levels of optic atrophy in primary progressive patients in the face of relatively poor visual function as previously mentioned may further hint at the dissociation between inflammation and dysfunction. If primary progressive disease is essentially prototypical multiple sclerosis, with secondary progressive disease being identical save for an ultimately inconsequential pro-dromal relapsing phase, then it is reasonable to suppose that the clinical difference between them represents the legacy of the relapsing remitting phase. Our study suggests this amounts to decreased superficial sensation in the lower limbs and a higher incidence of asymptomatic optic atrophy. Neither of these findings is likely to significantly affect the EDSS, especially at higher disability levels and thus our findings are consistent with large natural history studies[10;11] that indicate that acute relapses have little or no effect on long term disability.

In summary, the majority of central nervous system pathways display clinical signs of damage dependent upon the development of either primary or secondary progression. However, some central nervous system pathways appear to be more sensitive to the overall disease duration. Males appear to develop signs of corticospinal dysfunction more frequently and rapidly than women. The disability in primary and secondary progressive disease appears to be qualitatively similar apart from more frequent abnormalities of lower limb sensation and optic atrophy in secondary progressive disease.

Conclusions

(1) The majority of clinical signs in multiple sclerosis become evident in progressive disease.

(2) A few clinical signs become consistently evident before the onset of classical progressive disease, suggesting that secondary progression may be temporally dispersed and only frequently diagnosed when cortico-spinal tracts become involved.

(3) None of our patients had an EDSS of zero. Either remission is virtually never complete or insidious disease progression starts at the time of, or preceding the diagnosis.

(4) The finding of relatively infrequent optic atrophy in conjunction with relatively poor visual acuity in primary progressive patients suggests that optic neuritis may not be the dominant cause of poor visual acuity in multiple sclerosis.

Chapter 3: An analysis of relapse rate and quality in multiple sclerosis

Introduction

The presence of a sub-acute neurological deficit with subsequent remission in a young adult is highly suggestive of idiopathic demyelination[7]. A subsequent relapse disseminated in space is diagnostic of multiple sclerosis[15] where there is no reasonable alternative explanation. Approximately[10] 85% of multiple sclerosis cases begin in this relapsing-remitting fashion. Hence the relapse is usually the disease-defining event.

The English word 'relapse' derives from the latin word 'relaps' (slip again) which is the past participle of the verb 'relabi' ('to slip'). In relation to multiple sclerosis the **relapse** is defined in the McDonald criteria as an '*episode of neurological disturbance of the kind seen in MS, when clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature. Although there was some divergence of opinion, the group agreed that, for general diagnostic purposes, an attack, defined either by subjective report or by objective observation, should last for at least 24 hours*[13]*. This assumes that there is expert clinical assessment that the event is not a pseudoattack, such as might be caused by a change in core body temperature*[14] *or infection. Whereas suspicion of an attack may be provided by subjective historical reports from the patient, objective clinical findings of a lesion are required to make a diagnosis of MS. Single paroxysmal episodes (eg, a tonic spasm) do not constitute a relapse, but multiple episodes occurring over not less than 24 hours do.*'[15] The requirement for symptoms to last for greater than 24 hours is an attempt to discount 'pseudo-relapses' which may be caused by a transient rise in body temperature[14] associated with hot weather, exercise or fever.

(i) The pathology of relapse

The relapse is the clinical embodiment of an acute pathological event: plaque formation[50;59]. The histological changes associated with the hyper-acute stages of plaque formation remain the subject of much interest[3]. However the principle that acute plaque formation is more common in peri-venular distributions and involves local breakdown of the blood-brain barrier with ensuing infiltration of lymphocytes, macrophages and microglia leading to comprehensive demyelination and a lesser degree of axonal transection is generally accepted[7]. The mechanisms relating to clinical remission variably involve remyelination, neuronal plasticity and resolution of inflammatory conduction block with dispersion of voltage gated sodium channels along demyelinated axons to restore salutatory conduction.

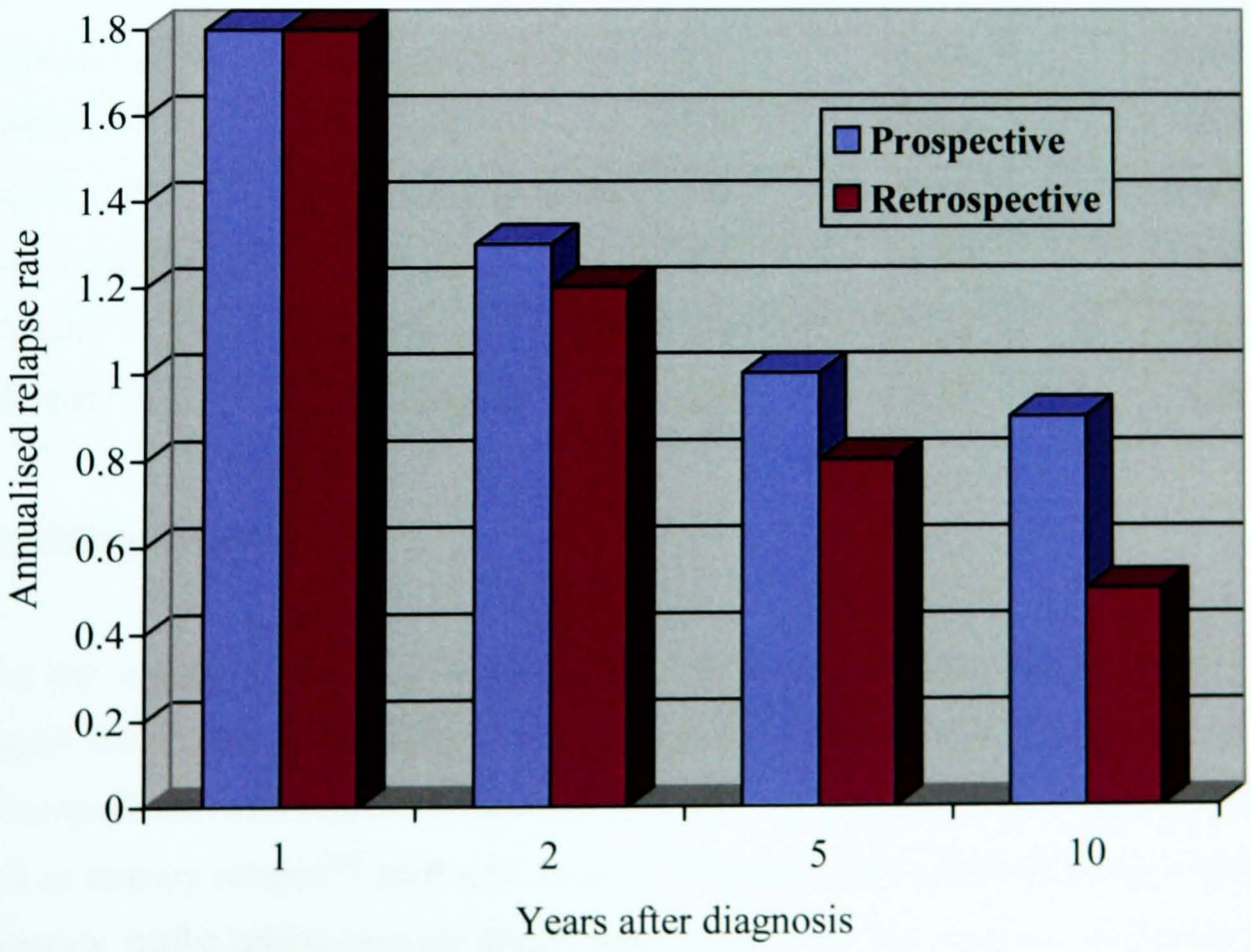
MRI studies reveal that the rate of new plaque formation in multiple sclerosis is ten to fifteen times higher than observed clinical relapses[7;63] and explanations for this would include plaques affecting clinically non-eloquent pathways, luxury neurological function[58] and incomplete ascertainment of minor relapses. An increased rate of new plaque formation at the time of clinical relapse has also been described[164] and whilst occasionally the relapse is poly-symptomatic and all identified new plaques are clinically apparent, often the relapse causing plaque is identified in association with new asymptomatic plaques. This suggests a systemic change at the time of relapse.

(ii) Relapse rates

The frequency with which relapses occur has been the subject of several **natural history** studies[10;157;165-168]. Despite broad agreement on the definition of a relapse[16] there is considerable variation in reported relapse rates. The range of reported relapse rates extends from the 0.14 relapses per year found by Gudmunsson[166] in 90 patients to the 1.1 relapses per year found by Patzold[168] in 102 patients with multiple sclerosis. Other relapse rate estimates include 0.86 relapses per year in relapsing-remitting disease and 0.31 relapses per year including all progressive disease types[121]. These dramatic variations are likely to be due to a synergistic combination of real phenomenon and systematic inequalities.

Natural history studies indicate that relapse frequency is highest early in the disease and decreases over time[167;168]. Prospective studies invariably report a higher relapse rate[165;168] than their retrospective counterparts, however it seems that the relapse rate in the first few years after diagnosis is similar whether assessed retrospectively or prospectively[168]. In Patzold's study of 102 patients with MS the relapse rates in the first year after diagnosis were 1.8 for both prospectively and retrospectively assessed patients. In the second year the relapse rates were 1.3 in the prospectively assessed group against 1.2 in the retrospectively assessed group, however, by the tenth year the prospective relapse rate was 0.9 against a retrospective relapse rate of 0.5 (see figure 3-1). Thus retrospective assessment of relapses seems to underestimate the relapse frequency at later disease stages only. This may be related to the higher attention to detail in documentation around the time of diagnosis where follow up may be more frequent: indeed relapse rate has been positively correlated with frequency of follow up[165]. In addition patients may paradoxically have a more detailed memory for their chronologically more remote early disease course.

Figure 3-1: Annualised relapse rate in 102 multiple sclerosis cases depending on time from diagnosis and assessment method (adapted from Patzold et al 1982[168])



Accepting the heterogeneity in the results of natural history studies, the general consensus is that, in a geographically based population of multiple sclerosis patients the annualised relapse rate would tend towards 0.5[169].

Relapse rate has proven to be a popular and intuitively logical primary outcome measure in **therapeutic trials** for multiple sclerosis. Indeed relapse rates are one aspect of the clinical natural history of multiple sclerosis that current 'disease modifying drugs' have an unequivocal effect on, at least for the first year[108]. The placebo arms of treatment trials have also yielded significant data with regard to relapse rates (see Table 3-1). It must be remembered however that these patients have frequently been selected for a high pre-trial relapse rate and so are not representative of an ideal natural history cohort. Table 3-1 shows a higher relapse rate in the placebo groups than would be expected in an unselected multiple sclerosis population and this is likely the result of systematically selecting patients with a high pre trial relapse rate.

Table 3-1: The annualised relapse rates from MS treatment trials

Study	Drug	Annualised relapse rate		p-value
		Active drug	Placebo	
Johnson et al[106]	Glatiramer acetate	0.59	0.84	0.007
BDMSAT[101]	Azathioprine	0.73	0.83	>0.05
Jacobs et al[8]	Interferon-β-1a (im)	0.67	0.82	0.04
IFNB study group[170]	Interferon-β-1b	0.84	1.27	0.0001
PRISMS[171]	Interferon-β-1a (sc)	0.86	1.28	<0.005
AFFIRM[172]	Natalizumab	0.22	0.67	<0.001

(iii) Relapse quality

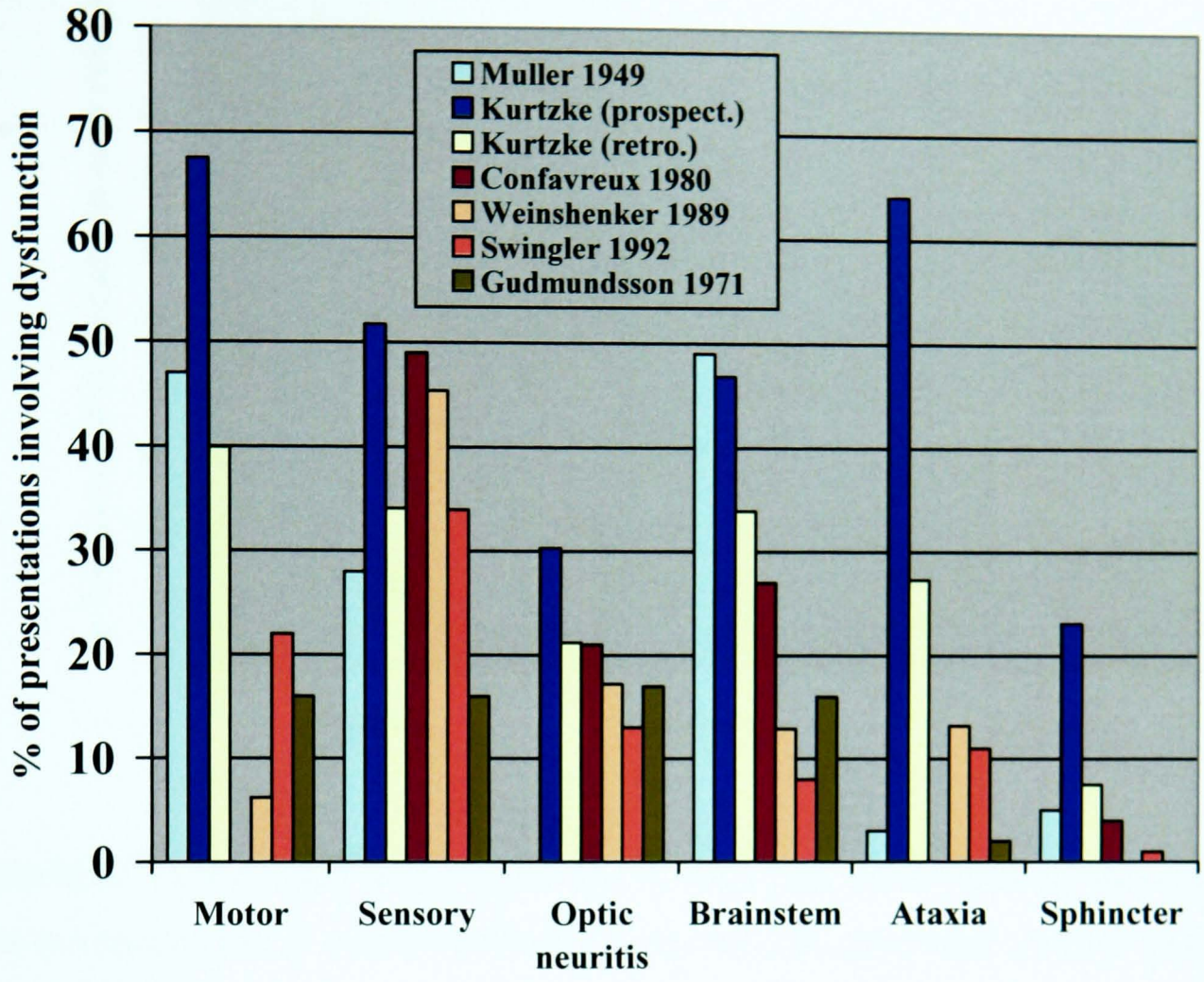
Does the quality or character of the relapse really matter? After all several studies suggest that overall relapse frequency and degree of recovery from relapse appears to be insignificant with regard to future prognosis[6,173]. However certain relapse types such as sensory relapse[158] and optic neuritis[174] are generally associated with a better prognosis whilst others provide data[30] supporting a role for relapses in permanent

disability formation. Furthermore with regards to large, partially prospective natural history studies[17;120] and treatment trials[8;106;170;171] the relapse is generally considered to be a binary all or nothing phenomenon. To individual patients the quality of a relapse does matter: optic neuritis is an entirely different experience than a paraparesis. The grouping of pathologically similar but clinically dissimilar phenomenon is only partially sensible. Myocardial infarction, stroke and peripheral vascular disease share pathogenesis but may result in markedly different clinical phenomenon and their combined assessment would usually be inappropriate – particularly where one was looking to examine the chronic disability produced by these diseases. Similarly one would not expect optic neuritis to lead to a chronic paraparesis or an acute cord lesion to result in chronic visual failure. Crude relapse counts ignore this critical nuance.

Several studies have detailed the quality or character of relapse in multiple sclerosis[17;121;159;175;176]. Comparison between different studies is hampered by a heterogeneous approach to assessment of relapse quality despite good agreement on the definition of a relapse[16;177]. Most studies have recorded details of the first relapse[121;159;176] or clinical presentation[17], which often inspires more detailed and precise record keeping as the clinician considers the differential diagnosis. Some studies have in addition recorded the quality of the subsequent relapses[121;159].

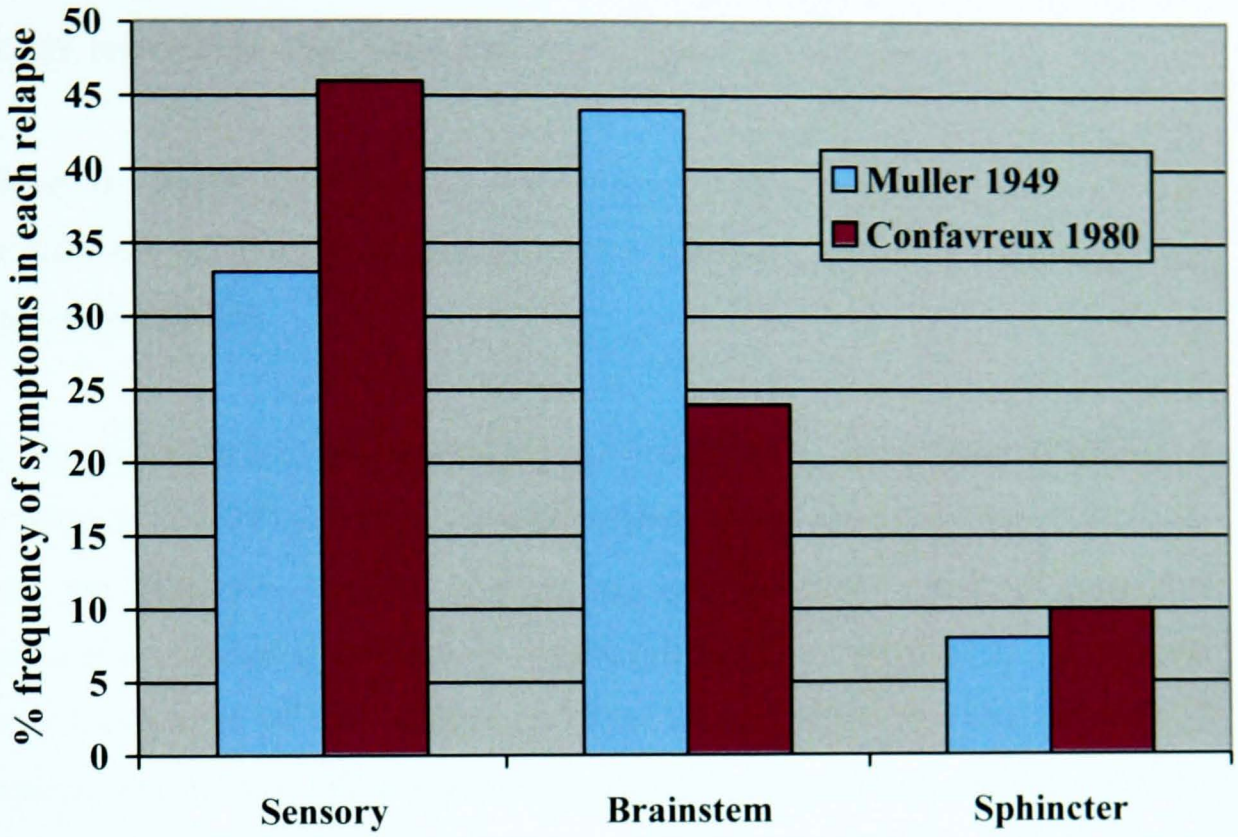
The literature pertaining to relapse quality provides highly heterogeneous results that are likely the result of variable methodology (see figure 3-3). The only area where a degree of homogeneity is achieved is in sensory symptoms and optic neuritis, which may be less ambiguous than other categories such as ataxia and motor dysfunction that can be partially interdependent. Another problem with these comparisons is the different methods of lumping and splitting employed by various researchers. Most researchers deal with symptoms[113;121;159]; or both symptoms and signs seperately[176]; whilst others group symptoms and signs together[17].

Figure 3-3: Initial presentation of relapse onset MS patients from 6 natural history studies[17;113;121;159;166;176]



To produce figure 3-3 it has been necessary to re-interpret result categories for the sake of comparison: for instance Muller[159] recorded cranial nerve symptoms, whilst Swingler[113] reported several distinct symptoms referable to the brainstem (of which oculomotor disturbance (8%) was by far the most common) and not brainstem signs. In several areas figures have not been obtainable by reasonable re-interpretation of categories. In no cases is there an incidence of zero therefore where a study has no representative bar this is merely an indication we found their data to be incomparable. Attempting to obtain figures from these particular studies for all prevalent relapses is even more challenging (see figure 3-4) as this aspect has not been reported in three of the studies[22;113;176]. Of the remaining two studies only three categories have been recorded in a manner that bears reasonable comparison – sensory, brainstem and sphincter symptoms.

Figure 3-4: Relapse quality in 2 cohorts of MS patients[121;159]



Confavreux[121] has divided motor symptoms at onset into those affecting upper and lower extremities and so cannot be directly compared with other studies which do not make this distinction. Also this study does not attempt (perhaps wisely) to distinguish motor and ataxic dysfunction.

The London, Ontario natural history study of 1099 multiple sclerosis patients[17] has recorded data on the initial clinical presentation of their patients These data do however include 205 patients (18.7%) who were progressive from onset and whilst they do record the distinction between acute motor onset and insidious motor onset it does not distinguish acute and insidious onset for sensory, brainstem, ataxic or visual symptoms. The case assessment of the London Ontario cohort, although not entirely prospective, has been validated by means of a rigourous geographical subset (the Middlesex County) and a seen from onset subgroup. With regards to the initial presentation the authors reveal very similar data from these control subgroups[17] which suggest their data is practically prospective. However, their figures are generally substantially lower than the truly prospective study of Kurtzke who had access to 476 soldiers in the American army with definite MS[176]. Two thirds of Kurtzke's cases of MS developed during the 2nd World War when a diagnosis of MS was sufficient for medical discharge from the army. Even though this meant missing

out on a working holiday on Omaha beach there may have been a tendency for even genuine MS sufferers to over report symptoms and exaggerate signs.

In addition to revealing information on relapse quality Figures 3-3 & 3-4 also disclose the very substantial complexity and discordance within the literature with regard to relapse quality.

The discrepancy between the clear effect of current disease modifying therapies on relapse but lack of effect on chronic disability progression may be related to an over-simplistic but ubiquitous practice of recording only the quantity and not quality of relapses, in turn explaining our lack of understanding of the relationship between the neurological character of each relapse and later chronic disability. Our first step in attempting to explore this relationship was to define and analyse the clinical features of disability in our cohort of patients and this is presented in Chapter 2. Our next step is to define and analyse the clinical features of each relapse in our cohort of patients and this is presented here.

Methods

The database of 150 patients with multiple sclerosis described in Chapter 2 was analysed. The nine patients with primary progressive disease had suffered no relapses and were excluded from this analysis. Relapse details were obtained by interview with the patient and detailed examination of the case records. For each relapse the date of onset was recorded. An attempt was made to characterise the quality of each relapse. For each relapse the following lateralising characteristics were recorded if present:

Deficit	Eye		Face		Arm		Leg	
	Right	Left	Right	Left	Right	Left	Right	Left
Optic neuritis			▒	▒	▒	▒	▒	▒
Weakness	▒	▒						
Sensory	▒	▒						
Ataxia	▒	▒	▒	▒				

Additionally the following non-lateralising relapse qualities were also recorded:

- Sphincter symptoms (bladder or bowel)
- Oculomotor symptoms
- Vestibular symptoms
- Bulbar symptoms

These categories are similar to those employed by the European Database for Multiple Sclerosis[29] but we have also recorded the specific limb involvement where applicable. Obviously an individual relapse could have more than one of the above qualities.

All assessments were carried by out by either Dr Luke Bennetto or Dr Janice Burrow, both of whom have several years of experience in taking a history and performing neurological examination.

Comparison of frequency of relapse qualities between sexes and disease sub groups was assessed using Fisher's exact test.

Results

Of the 150 patients on the database 9 were excluded as they had primary progressive multiple sclerosis and no relapses. 141 patients were analysed of whom 103 were in the relapsing remitting stage whilst 38 were in the secondary progressive phase. 109 of these patients were female whilst 32 were male. See Chapter 2 for basic demographic details.

(i) Relapse rates

Figure 3-5: Mean total relapse counts and disease duration (n=141)

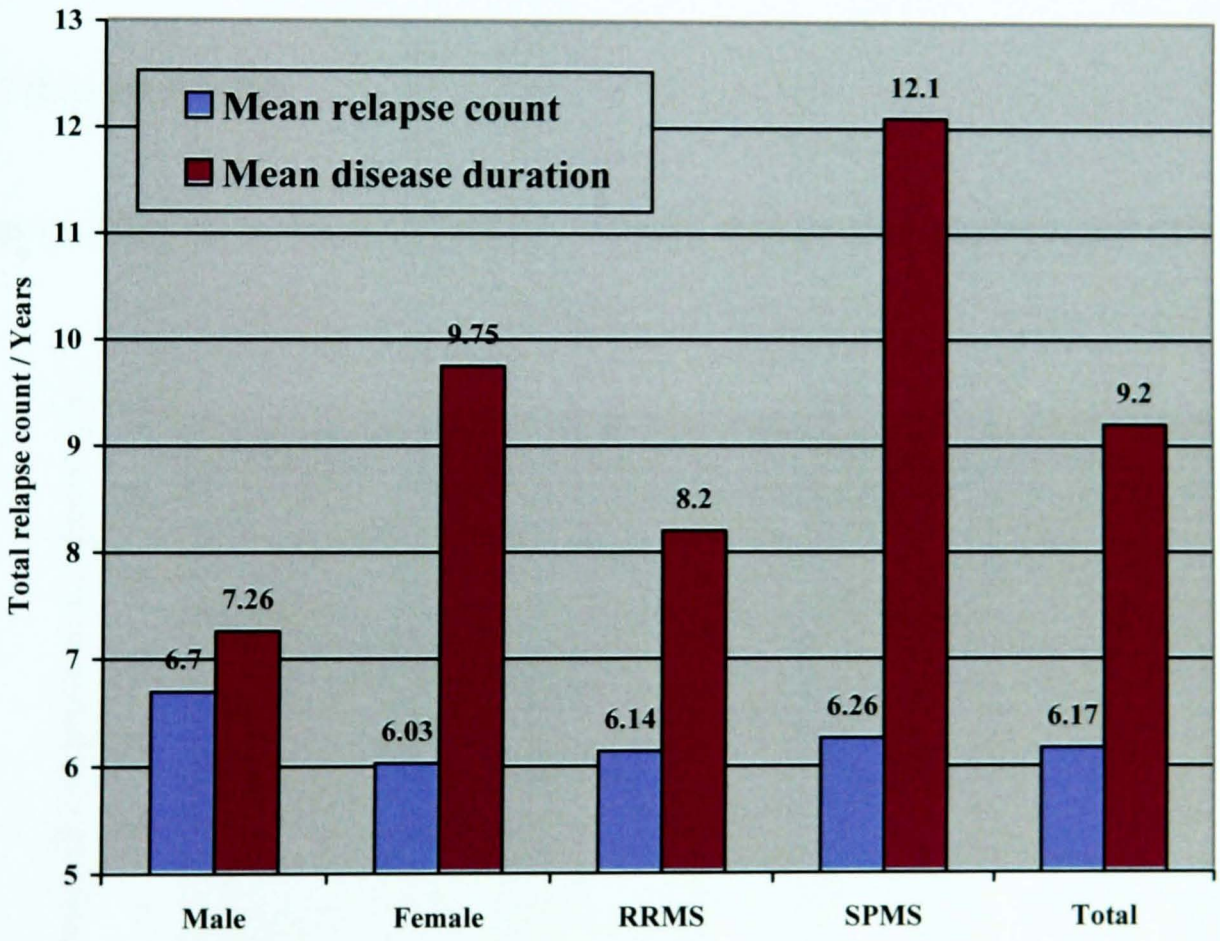
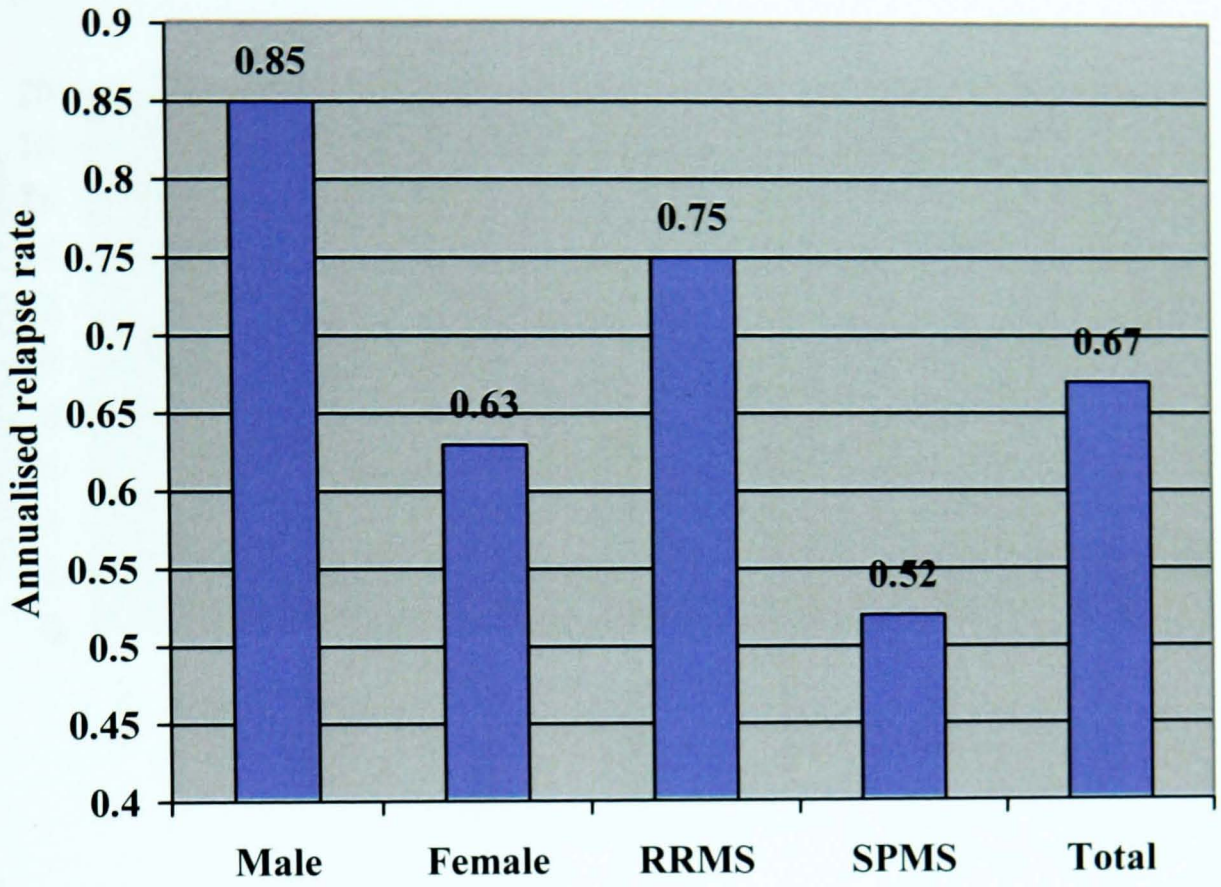


Figure 3-6: Annualised relapse rates over total disease duration (n=141)



(ii) Relapse quality

Figure 3-7a: % incidence of motor, sensory and ataxic symptoms per relapse

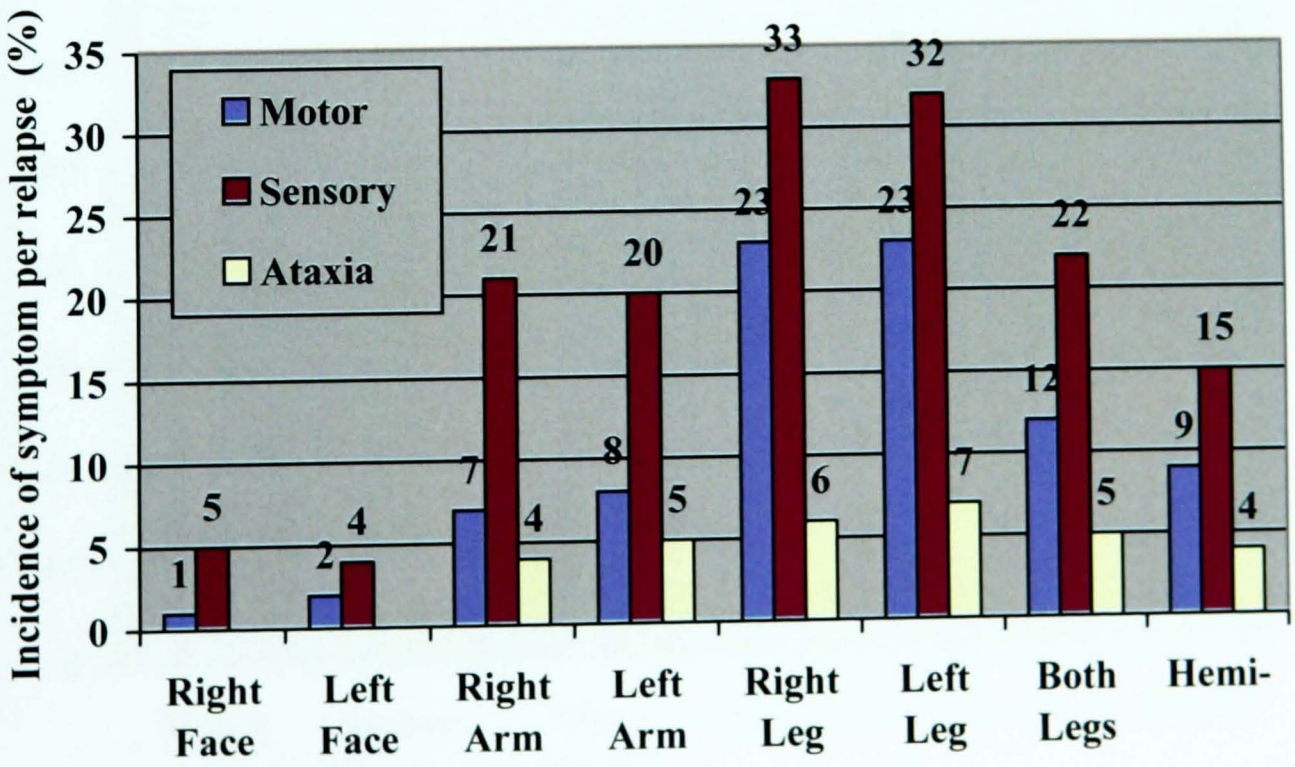


Figure 3-7b: % frequency of visual, brainstem and sphincteric symptoms per relapse

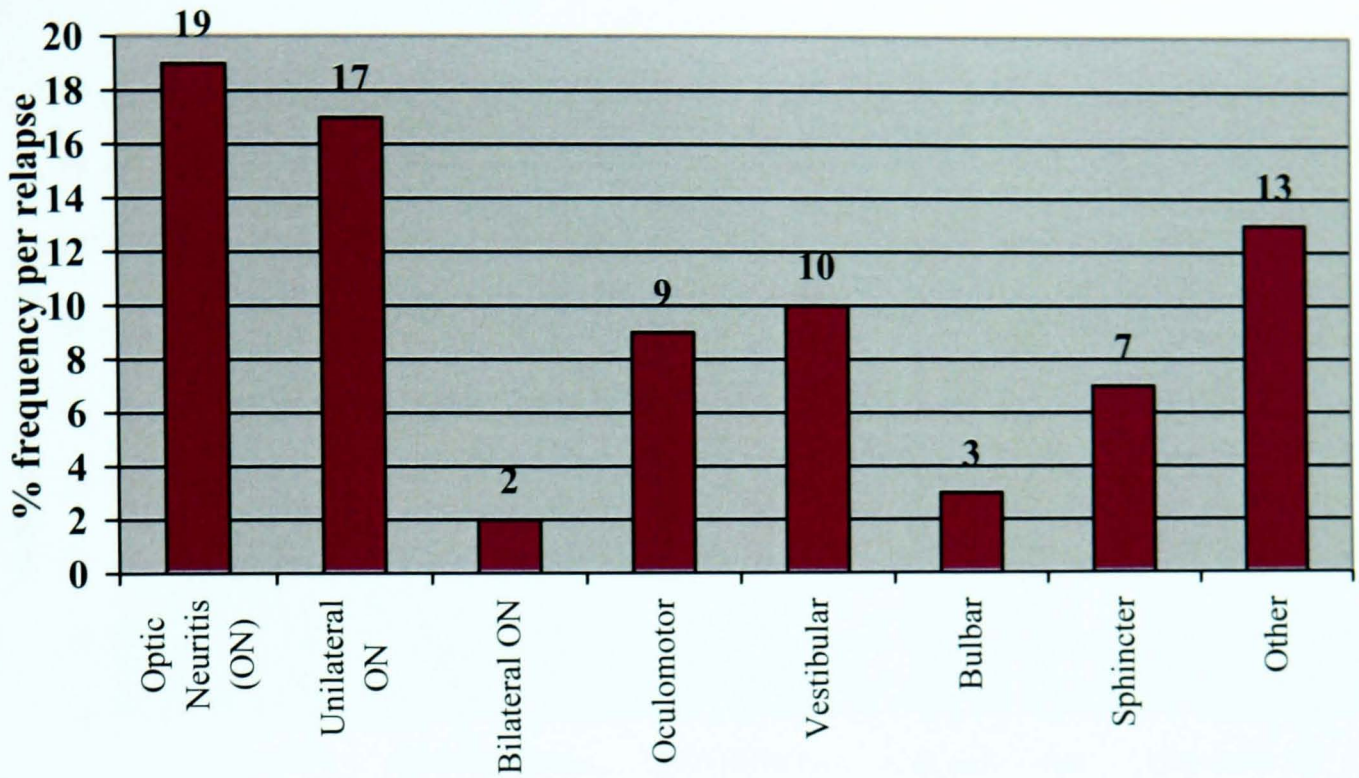


Figure 3-8: An approximate comparison of relapse quality between our cohort and other studies

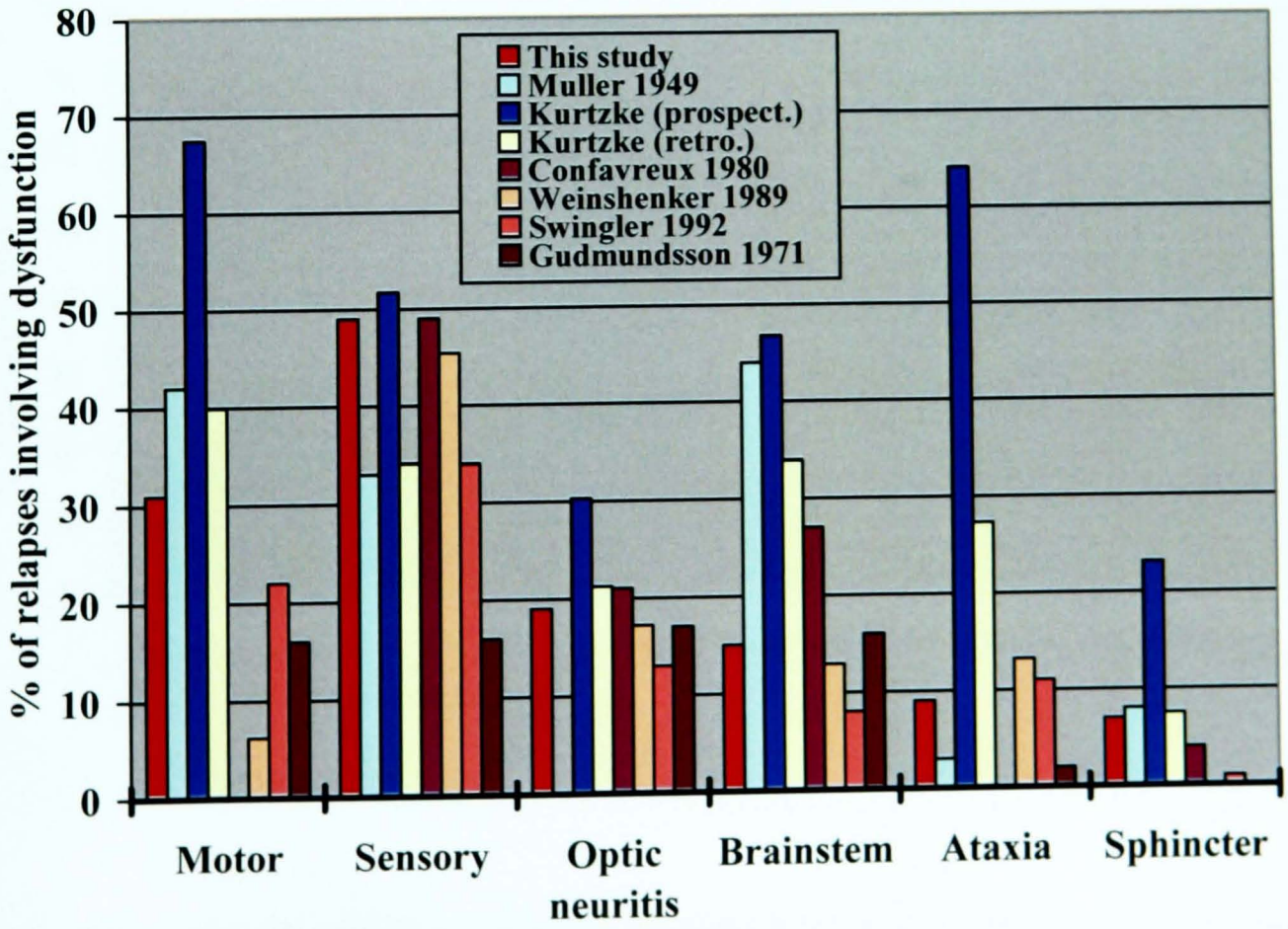


Figure 3-9a: % frequency of optic neuritis and limb symptoms per relapse according to gender

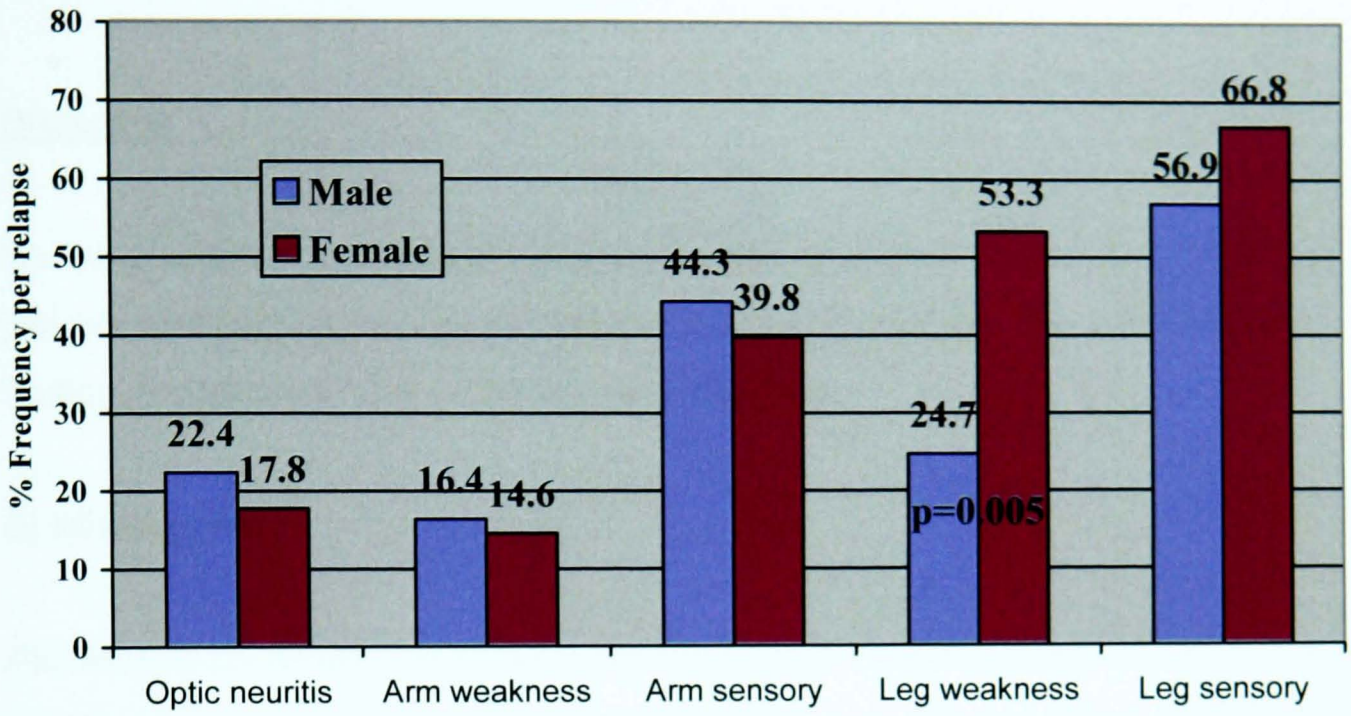
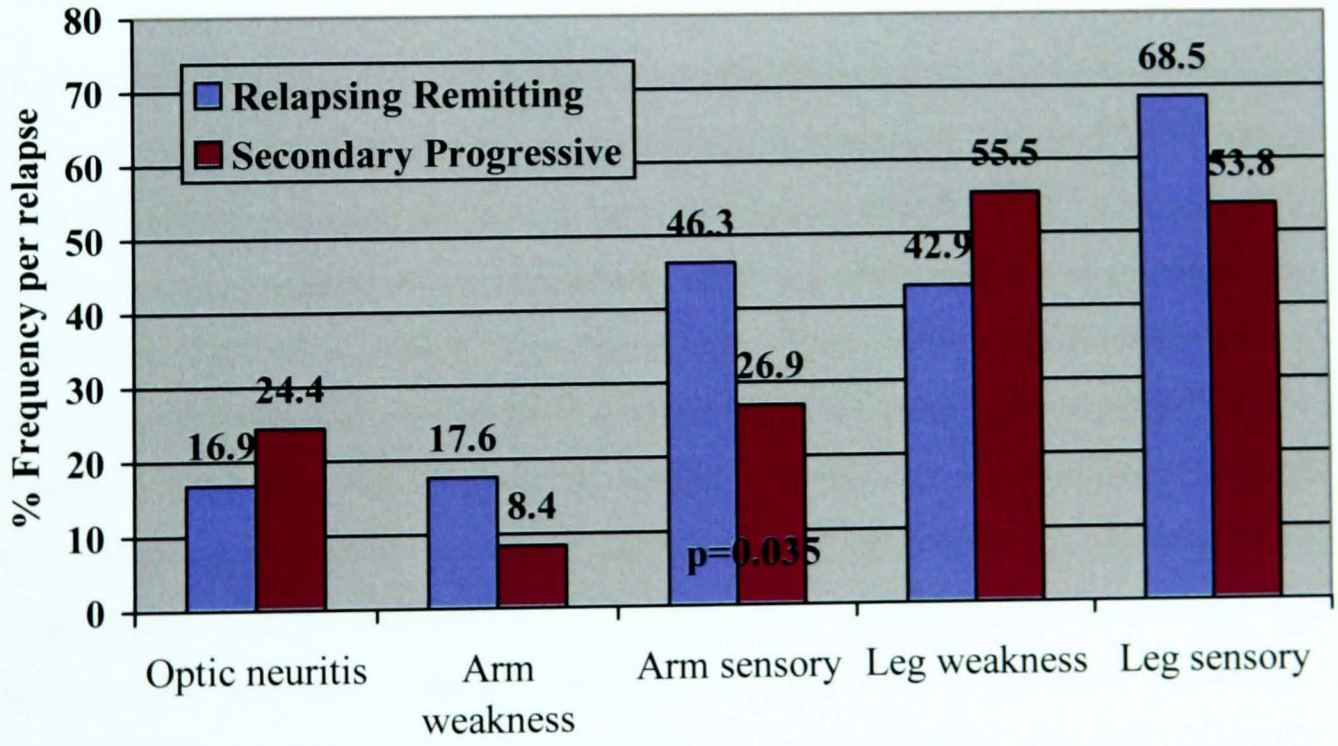


Figure 3-9b: % frequency of optic neuritis and limb symptoms per relapse according to disease sub-type



Figures 3-9a and 3-9b pertain to episodes of unilateral limb or eye symptoms and so figures are higher than where the laterality data is presented separately. Bilateral leg

weakness is recorded as 2 episodes of unilateral leg weakness and it is therefore worth noting that figures of up to 200% are technically possible in these figures.

Discussion

We have obtained retrospective quantitative and qualitative relapse data from 141 patients with McDonald criteria relapse onset multiple sclerosis. We will discuss our findings for relapse rate and relapse quality separately.

(i) Relapse rate

The annualised relapse rate of 0.67 (see figure 3-6) compares reasonably well with other studies. As previously mentioned published figures for annualised relapse rate range from 0.14[166] to 1.1[168] in natural history studies and from 0.67[172] to 1.28[171] in the placebo arms of treatment trials. Two factors likely explain our figures being slightly lower than the average placebo arm.

Firstly all of the patients in the placebo arms of treatment trials had been selected by virtue of a high pre-trial relapse rate (usually 2 in preceding 2 years)[8;170;171] which has been shown to correlate with a high subsequent relapse rate[178]. Our patients, however, were recruited at the assessment stage for which there was no minimum relapse rate although it is likely there was a referral bias towards higher relapse rates. Secondly our study was retrospective as opposed to the prospective treatment trials. However, accepting that prospective studies will always be preferable to their retrospective counterparts we are reassured by the proximity of our annualised relapse rate to those reported in the prospectively assessed treatment trials. We believe this provides notional validation of our data collection techniques. Anecdotally record keeping was generally of a high standard and patient history often supported by meticulously kept, if slightly dated diaries.

The lower annualised relapse rate of secondary progressive patients (0.52) compared with their relapsing-remitting counterparts (0.75) is mainly a result of a longer follow up period extending into the secondary phase of disease where relapses are much less

frequent[7;179]. The longer disease duration in secondary progressive patients also increases the amount of retrospection required with an inevitable, albeit hopefully small, loss of data integrity[168] (see figure 3-1).

The slightly higher annualised relapse rate in males (0.85 vs 0.63) is partially explained by their having been assessed comparatively early in the disease course (see figure 3-5). In contrast to our findings research on the placebo arm patients from treatment trials suggest that the relapse rate is higher in females[179]. Certainly whilst men are widely reported as having a worse prognosis[156;157;157;174] it is not clear that this is a result of more frequent relapses. It is possible that our findings may have their roots in the lower than expected number of men in our cohort. According to natural history data[17;25;121;180] we should have approximately 50 men in a sample of 150 patients. The fact that we had only 34 may have been a result of a relative reluctance of men to be assessed for treatment in turn meaning that there was a relative referral bias towards males with particularly high relapse rates.

(ii) Relapse quality

Our results (see figure 3-7a) indicate that relapse quality in the face and limbs frequently involves sensory disturbance over motor dysfunction. Limb ataxia in relapse seems to be a relatively infrequent phenomenon in this retrospective assessment. An approximate ratio of frequency of ataxic:motor:sensory relapse would be 1:3:5. Similarly episodes of sensory and motor relapse become progressively more frequent in more distal body structures with a topographical ratio for face:arm:leg of about 1:5:10.

We believe it is reasonable to assume that relapses have no inherent tendency to lateralise to one particular *side* of the body or nervous system except by chance. We present our lateralised data in figure 3-7a. This may act as partial validation for our data ascertainment by revealing very similar figures for left and right sided relapse. If the study were too small then clear differences in laterality may be evident by chance.

Figure 3-7b shows the frequency of visual, brainstem and sphincter symptoms per relapse. As has already been discussed comparison between existing studies is difficult due to variable methodology and results therefore can seem to be disparate (see figure 3-3). In figure 3-8 we attempt to compare our results with others. It should be noted that like is not strictly being compared with like as several approximations have been required to enable a visual comparison of the data. As previously described some studies were prospective[176] while most were largely retrospective. The majority of the data presented pertains only to the initial relapse or presentation where our study and two others[121;159] pertain to all relapses. Our own data has had to be recalculated in a lower resolution format that bears comparison. Therefore it would be wrong to draw strong conclusions from figure 3-8. However despite the inherent heterogeneity of this data we believe our own figures compare reasonably well: all of our data is bounded both above and below by other study results and we have no outliers.

(iii) The effects of gender and disease subtype on relapse quality

Next we have sought to examine whether gender and disease sub-type have any effect on relapse quality. For this purpose we have not analysed uncommon symptoms to reduce the possibility of false positive errors.

Figure 3-9a compares the frequency of these symptoms per relapse between males and females. Results are generally comparable except leg weakness which is much more frequent in female relapses (53.3% vs 24.7%, p=0.005 using Fisher's exact test). This result was not expected from the literature although we could find no previous work that had addressed the issue of relapse quality according to gender. Quite why leg weakness should be more common in female relapses whilst the other relapse qualities are comparable is unclear. It is possible that these findings are related to systematic differences between the sexes in the way they interact with healthcare provision and report relapses – although if this were the case perhaps one would expect to see significant differences across all the relapse qualities examined. In addition from previous work we know that gender clearly does modulate the phenotype of multiple sclerosis. Mutliple sclerosis is approximately twice as common in females[17;121] and tends to have a worse prognosis and start later in

men[17;181], also primary progressive disease is relatively more common in men[5]. As other sex differences in multiple sclerosis[145;150] are probably attributable to sex hormones such as testosterone and oestrogen we assume this may underlie this observation also although less likely possibilities could include factors associated with pregnancy and parturition including epidural anaesthesia. Further research, with an *a priori* hypothesis would be required to validate this observation.

Figure 3-9b compares relapse quality between secondary progressive and relapsing remitting patients. This shows that relapses involving sensory disturbance in the arms are more frequently recorded in relapsing remitting patients than in secondary progressive patients. This is of some interest as even in the secondary progressive patients the vast majority of the relapses recorded had occurred during the relapsing-remitting phase of the disease.

There are two possible explanations for this observation. Firstly it may, partially at least, be an artefact of the longer disease duration and cognitive decline occasionally found in secondary progressive patients with relatively poor recall of early disease events. This problem is certainly not new in natural history studies of MS. The London, Ontario study[17] found that 30% of patients who were assessed retrospectively reported progressive disease from onset whereas 15% of patients who were seen by a neurologist from disease onset reported that their disease was primarily progressive. The authors believe this "disparity possibly reflects a tendency for patients who are seen for the first time at a later point in their illness to discount or forget earlier remitting symptoms when progressive disease intervenes subsequently"[17]. We accept this is possible within our own cohort but believe it unlikely to be a significant factor as a large majority of the patients had been seen from onset by the local clinical institutions and early relapses were frequently confirmed by examination of the case records.

Another possibility is that sensory relapses may be neutral or even in effect protective against the onset of secondary progression. Sensory relapses have been shown to be a favourable prognostic factor in many studies but so has optic neuritis [182;183] which in our study was found more frequently in secondary progressive patients. The mechanisms by which sensory relapses and optic neuritis might

predispose to a favourable course are unclear and may partially relate to the frequent use of the EDSS and DSS [18;19] that places a heavy emphasis on mobility which is less likely to be affected by sensory or visual disturbance.

Alternative explanations would include an MS phenotype that largely spares motor, but not sensory or optic, nerve fibres. Certainly there is a precedent for MS phenotypes with anatomical bias: oriental MS[125] is typically optico-spinal in distribution. The possibility that the clinical quality of relapses represents more than just a random occurrence of symptomatic demyelination exists. We know that plaque distribution generally observes certain macroscopic patterns: peri-venous, peri-ventricular, cortical u-fibres, brainstem, optic nerves and spinal cord[7]. Might more subtle MS phenotypic variation also have a preference for individual fibre types and in turn relapse quality?

Conclusions

- The annualized relapse rate of 0.67 in our cohort suggests good relapse ascertainment.
- In our cohort sensory symptoms are more frequent than motor symptoms.
- Comparison with previous studies is difficult but suggests our relapse quality data is both reasonable and broadly comparable.
- Leg weakness is a more frequent relapse quality in females.

Whilst these are interesting observations the main purpose for presenting this data is to allow the reader to make their own assessment of the validity of our retrospective relapse data. The quality of this data is critical for our attempt to correlate relapse quality with the findings of a subsequent prospective neurological examination.

Chapter 4: The relationship between relapse and disability in multiple sclerosis

Hypothesis: That in patients with multiple sclerosis, chronic disability correlates poorly with individual acute relapses.

Introduction

The precise relationship between acute clinical relapse and subsequent disability in multiple sclerosis is unknown. It is widely believed that relapses confer a poor prognosis and shape future disability[7]. Recent evidence suggests this may not be the case. Patients who have primary progressive disease and therefore little or no relapse activity accumulate disability more rapidly than patients with relapsing onset disease[10;129]. Relapses during the secondary progressive phase do not appear to be detrimental[10] to prognosis. The acute central nervous system inflammation associated with clinical relapse in multiple sclerosis is known to have both harmful and beneficial sequelae[26;28]. If clinical relapse is not the determining pathological process in multiple sclerosis then one might expect to see qualitative discordance between relapse and subsequent disability in the same individual over time.

The later stages of multiple sclerosis are frequently characterised by marked disability. After 30 years disease duration most patients have been found to be wheelchair dependent[10]. The majority of the morbidity associated with multiple sclerosis is likely to come from these latter stages of fixed disability as compared to the earlier stages of relapse and remission. The relationship between relapse and long term disability is unclear.

Magnetic resonance imaging studies have confirmed the association between acute relapses and the formation of sclerotic plaques[50;60;135]. Sclerotic plaques are characterised by demyelination, axonal loss and gliosis. Reparative mechanisms including remyelination, ion channel redistribution and plasticity, whilst forming the basis of remission, are rarely complete. Neurological transmission through a sclerotic

plaque is therefore impaired. Intuitively sclerotic plaques should lead to the chronic neurological impairment that forms the basis of disability.

It has long been noted, however, that the function of pathways that are involved in the sclerotic plaque survives surprisingly well considering the evident histopathological devastation that has occurred. Charcot in 1877 noted[7]: "Amblyopia is a persistent and frequent symptom of cerebro-spinal disseminated sclerosis but it rarely issues in complete blindness. This is worthy of notice since patches of sclerosis have been found after death occupying the whole thickness of the nerve trunk, in the optic nerve, in cases where during life an enfeeblement of sight simply had been noted. This discrepancy between symptom and lesion constitutes one of the most powerful arguments to show that the functional continuity of the nerve tubes is not absolutely interrupted although these, in their course through the sclerosed patches, have been despoiled of their medullary sheaths and reduced to axis cylinders." In comparison with other central nervous system lesions, such as infarction or trauma, individual episodes of multiple sclerosis type demyelination have an excellent prognosis.

Müller reported on 810 Swedish patients with multiple sclerosis in 1949[159]. He categorised clinical episodes or 'bouts' into either remittent bouts (relapses) or progressive bouts (disease progression). Muller noted (see Table 4-1) that the progressive bouts frequently involved motor disturbances (91%) but rarely involved cranial nerves (9%) or sensory disturbance (20%). This is despite the fact that remittent bouts involving cranial nerves (44%), motor disturbance (42%) or sensory disturbance (33%) occurred with similar frequency. Also although 21% of monosymptomatic remittent bouts feature an isolated disturbance of sensation they did not record a single progressive bout featuring sensory disturbance alone. This compares with isolated motor disturbance occurring in 26% of monosymptomatic remittent bouts but 86% of monosymptomatic progressive bouts. The conclusion that remitting bouts and progressive bouts appear to be unrelated phenomena was not made. According to this data it is hard to believe that the relapses are acting as a template for secondary progression. Perhaps in the prevailing scientific climate such results might have been seen only as an indication of methodological flaws rather

than a true dissociation between relapse and progression, a notion that has gained virtually unanimous support[10].

Table 4-1: Frequency of certain symptom groups in progressive, remittent and first bouts in 810 Swedish patients[159]

		Symptom groups						
		Cranial nerves (%)	Motor (%)	Sensory(%)	Sphincter(%)	Other(%)	Paretic(%)	Intention tremor or dysmetria (%)
		Progressive Bouts						
Total Bouts	707	9	91	20	33	15	74	24
Mono symptomatic	343	3	86	0	6	5	-	-
Poly-symptomatic	364	15	96	40	55	23	-	-
		Remittent bouts						
Total Bouts	2957	44	42	33	8	2	29	3
Mono symptomatic	2196	46	26	21	5	2	-	-
Poly-symptomatic	761	40	87	68	18	5	-	-
		The first bout						
Total bouts	793	49	47	28	5	2	33	3
Mono-symptomatic	590	51	31	16	1	1	-	-
Poly-symptomatic	203	42	91	62	15	5	-	-

Notwithstanding what we would describe as these clear signposts, the widespread belief that "Secondary progressive multiple sclerosis tends to affect whichever system has borne the brunt of the disease earlier in the course"[7] remains as popular as it is intuitive. We hypothesise that individual episodes of relapse in multiple sclerosis are not the cause of chronic impairment and disability. We aim to explore this by comparing the relapse history of a group of patients with multiple sclerosis and comparing this with a contemporary clinical examination. Certainly (as Muller found) cranial nerve and sensory deficits rarely progress despite the fact that these systems frequently bore the brunt of the earlier disease course. McAlpine and Compston[167] similarly found that isolated sensory symptoms were common during the relapsing-remitting disease phase (41 out of 146 patients) but were rare as an isolated chronic progressive symptom (1 out of 146 patients).

A recent study[30] sought to examine the effects of a relapse on disability. Data analysed from 224 patients randomized to placebo in previous therapeutic trials revealed that 42% of their patients had a worsening of at least 0.5 EDSS points at an average of 64 days post relapse. The average EDSS change amongst the whole group was an increase of 0.27 EDSS points. Although not commented upon their data also reveal that 58% of patients have a stable or improved EDSS following a relapse. The authors conclude[30] that this demonstrates relapses produce a measurable and sustained effect on disability. This appears consistent with models suggesting that disability during the relapsing remitting phase is accrued by virtue of incomplete remission. This study has limitations however. A longer follow up with blinding of examiners to the clinical history and a control group of multiple sclerosis patients who had not suffered recent relapse would allow determination of whether relapses truly contribute to fixed disability at a population level, whether they merely camouflage an early progressive phase[23] or prompt more detailed clinical examination of areas highlighted in the history. A history of optic neuritis obviously helps to reassure the examiner that slight disc pallor is a clinical sign rather a normal variant. The reliance placed on the EDSS for this study and not individual clinical signs, in contrast to our own study, means that it is difficult to be sure that the increase in post relapse EDSS is reflective of new deficits at the site of relapse.

The optimum method to assess the clinical legacy of an acute plaque in multiple sclerosis would undoubtedly be a prospective study design involving regular clinical assessment and imaging starting many years prior to symptomatic disease onset. The temporal association of plaque formation with clinical relapse quality would allow assessment of not only the radiological appearances of the plaque but also its resultant clinical effects to be charted over time. This approach would prevent the disappearing plaque[98] being disregarded. A plaque may presumably disappear by repair or atrophy. Single time point studies of MRI plaques and disability will obviously fail to register the disappearing plaque or the atrophied lesion load and will necessarily underestimate the chronic effects of the acute plaque.

The optimum study was not possible within the available time frame. A study with a degree of retrospective assessment is necessary to assess a practically time unlimited

disease within a limited time frame. A purely clinical approach allows clinically eloquent acute plaques to be recorded in the form of a history of acute relapses. The clinical nature of the relapse indicates the affected pathways. One assumes that plaques can only appear or disappear but not move within the central nervous system over time. Therefore if acute plaques are to be held responsible for chronic disability then the chronic disability will match closely the quality of the combined acute relapses.

The advantages of a historical clinical approach over a radiological approach to identifying the legacy of acute plaques are two-fold. Firstly the study is not confounded by disappearing plaques[98]. Secondly problems of relating plaque structure to disability are avoided. This problem is partly technical. Clinically eloquent areas with multiple small pathways beyond the accurate resolution of the MRI scanner such as the spinal cord[100] highlight this point. In the clinical study the chronic impairment should simply mimic the acute impairment.

The acknowledged disadvantages of the clinical approach over the radiological approach are principally that there are many more plaques than relapses in patients with multiple sclerosis[72]. However by assessing relapses one will identify the clinically eloquent plaques that are likely to represent more destructive acute pathology than the corresponding silent plaque. The caveat to the above is that historical data even when obtained from multiple overlapping sources including the patient history and hospital records is inherently imperfect. Despite extensive efforts it is clear that not every relapse will be recorded accurately.

Methods

The database described in chapter 2 was analysed. Briefly, patients with McDonald criteria[15] multiple sclerosis who were being assessed for their suitability for prescription of the disease modifying drugs beta-interferon and glatiramer acetate were examined and a clinical history and consent for the study was obtained. This information was recorded in a password protected computer database. 150 patients

were recruited to the study. For the purposes of this analysis the 9 primary progressive patients were excluded leaving 141 patients.

Statistical analysis

Our primary aim was to analyse whether a history of relapse in a particular limb or eye was associated with the presence of an appropriate clinical deficit at assessment. For several reasons a linear approach was considered sub-optimal. The limb specific data was recorded as part of the functional systems score component of the EDSS and included other ordinal and non-linear scales such as the Medical Research Council scale for measuring limb strength. For this reason a binary logistic regression analysis was used with each target limb or eye either considered to be appropriately impaired or not. The definitions used to dichotomise the data for each of the four examined systems are outlined below. The number of relapses per limb/eye was not normally distributed with a high proportion of zeros (see table 4-2) and for this reason the relapse data were transformed into three categories: none, one and many (see table 4-2). Factors such as the patients age, disease duration, sex and whether the patient were in the secondary progressive phase of the disease as well as limb related factors – arm or leg – were considered to be potential confounders and so were entered into the regression. Statistical analysis was performed using SPSS version 12 (SPSS inc., Chicago, IL) statistical package.

Binary impairment transformation

Limb weakness was defined by any score of 4+ or less as judged by the Medical Research Council grading system within any one or more of five separate movements in each limb. In the arm these included shoulder abduction, elbow flexion, elbow extension, wrist extension and wrist flexion. In the leg these included hip flexion, knee flexion, knee extension, ankle dorsi-flexion and ankle plantar flexion.

The presence of **cerebellar ataxia** in a limb was defined by the presence of tremor or clumsy movements seen easily with at least a minor interference with function and not felt to be attributable to a sensory ataxia.

The presence of **sensory disturbance** in a limb was defined by the patient being aware of impaired or absent light touch or pain on sensory testing. (Defined as mild abnormality or worse on Sensory Functional Systems Score component of EDSS). The superficial sensation component was chosen to define sensory disturbance over vibratory or proprioceptive loss as we felt this was more likely to correspond with the patient's description of sensory disturbance during a relapse. In addition previous analysis suggested abnormality of superficial sensation (see table 2-4, chapter 2) was present in nearly 40% and would be a relatively good discriminator in comparison to vibratory (very common abnormality) or proprioceptive (rare abnormality) impairment.

The presence of **poor vision** in an eye was defined by the presence of a corrected visual acuity of worse than 6/6 as defined by Snellen chart testing.

Results

A total of 150 patients with multiple sclerosis were recruited to the study, 9 of these were excluded from this analysis as they had primary progressive disease without relapse. The demographic and basic clinical details of this cohort are presented in Chapter 2 whilst further relapse data are presented in Chapter 3.

Table 4-2: The frequency of relapse types in cohort (n=141 patients)

Relapse type	Relapses per limb (n=564) /eye (n=282)				Mean relapses per limb/eye	
	None	**One**	Many	Range	All	Many relapse group only
Weakness	335	123	106	0-14	0.84	3.30
Cerebellar Ataxia	438	88	38	0-8	0.34	2.79
Sensory	168	181	215	0-11	1.56	3.10
Optic neuritis	174	80	28	0-8	0.57	2.92

Table 4-2 shows how many relapses of each type were suffered by each limb and eye in the cohort of 141 relapse onset MS patients. It largely echoes data presented in Chapter 3 which suggest that sensory relapses are more common than weakness relapses which are in turn more common than ataxic relapses.

Table 4-3: Multivariate analysis of potential risk factors for development of clinical impairment in multiple sclerosis (n=141)

Clinical factor		Clinical Impairment							
		Weakness		Cerebellar Ataxia		Sensory disturbance		Poor vision	
		p-value	OR	p-value	OR	p-value	OR	p-value	OR
Relevant relapse	One	0.894		0.08		0.003	2.073	0.012	2.27
	Many	<0.001	4.046	<0.001	6.15	0.001	2.188	0.022	2.992
Male sex		0.207		0.596		0.01	1.75	0.089	
Age (years)		0.046	1.028	0.013	1.038	0.974		0.858	
Duration (years)		0.479		0.163		0.052		0.021	1.06
SPMS		<0.001	2.839	0.001	2.18	<0.001	3.253	0.01	2.29
Leg		<0.001	3.485	0.001	2.24	0.54			

Binary logistic regression used to compare limbs or eyes with a particular impairment (weakness, ataxia, sensory or visual) with unimpaired equivalents. Comparator groups include female sex, RRMS and arm.

	P<0.05 primary outcome measure
	P<0.05 secondary outcome measure

Figure 4-3 reveals the relationship between relapse and subsequent relevant impairment of an individual limb or eye. Other factors such as the age, disease duration, sex, secondary progressive status and whether the limb is an arm or leg are entered into the analysis to try to account for these potential confounders.

Interestingly a single relapse involving limb weakness or ataxia does not appear to predispose to relevant chronic impairment although multiple weakness or ataxia relapses in the same limb are associated with relevant chronic impairment. This result suggests that it is more than one clinically eloquent plaque on an individual motor pathway that causes, or is related to, chronic weakness. An isolated clinically eloquent plaque does not appear to adversely affect the motor pathways long-term functional integrity. However sensory relapses and optic neuritis are associated with relevant chronic impairment after only the first relapse although the association is slightly stronger for multiple relapses.

Of the secondary outcome measures the presence of secondary progressive disease shows a consistent and strong association with specific impairment across all 4 domains.

Discussion

Interestingly we begin to see a plausible explanation for the dissociation of relapse from disability as presented in the large natural history studies. In general our results confirm the received wisdom that relapses are associated with relevant chronic impairment although with significant caveats: the motor pathways (pyramidal and cerebellar) appear to be resistant to a single relevant relapse. However this is quite different from suggesting that relapses cause disability as measured by the EDSS. The large natural history studies do confirm a relationship between relapse rates and assignment of an EDSS of 4 although the relationship is lost at greater EDSS scores[10]. Poignantly the EDSS is an impairment scale up to an EDSS of 4 but past this point it becomes a mobility scale. So these studies confirm our own findings that relapses are associated with impairment but they also suggest that relapse does not affect mobility: how can this be?

Firstly certain relapse types even when effecting chronic impairment are unlikely to translate into a loss of mobility. Sensory and visual systems would fall into this category. It would require a severe impairment of vision in both eyes to affect mobility but even the blind patient with appropriate guidance (not support) is not distance limited. Similarly even a marked sensory impairment is unlikely to impact significantly on the ability to walk unless perhaps combined with severe impairment in other systems – such as is usually only found in the secondary progressive stage of the disease. Thus sensory relapses and optic neuritis are likely to have significant traction on the EDSS scale at its lower levels where it is an impairment scale but little or no traction on the mobility portions of the EDSS scale. This is highlighted by the work of Lublin[30] who found that relapses did leave a sustained and measurable increase in EDSS but that there was a significant negative correlation between pre-relapse EDSS and post relapse residual EDSS, in addition the Scripps Neurological Rating[115] scale detected post relapse residual in a greater proportion of patients than did the EDSS further emphasising the greater traction of relapses on impairment

over mobility. Indeed Lublin[30] appears to have recognised that it may be the EDSS scale rather than multiple sclerosis that is insensitive to relapses at its later stages but he did not appear to relate this to the changeover from an impairment to mobility scale apparent in the EDSS.

Secondly certain relapse types, particularly optic neuritis and sensory relapses, have previously been associated with a relatively good prognosis in multiple sclerosis[158]. Accepting that reliable prospective indicators of 'benign multiple sclerosis' continue to prove elusive, this may suggest that there are further appropriate sub-divisions of multiple sclerosis[184] to place alongside the widely accepted optic-spinal[185;186] oriental variant of multiple sclerosis. Such subtypes may include sensory pre-dominant disease that may in any case be associated with a better prognosis. If this is the situation and one does not take into account the relapse quality but merely relapse counts then the situation is precarious: one patient may have many sensory relapses and low disability by virtue of their as yet undefined benign subtype and be compared with another patient who has had only two relapses, both of which involved leg weakness and who has a higher EDSS. Such an analysis whilst crude and illustrative might incorrectly conclude that relapses were inversely associated with disability in a dose related manner.

Thirdly, weakness and ataxia, the relapse types which would be expected to have real traction on the mobility portions of the EDSS, appear to have increased resistance to the long term sequelae of relapse: an individual weakness or ataxia relapse in a limb is not associated with relevant chronic impairment. Whether this represents an evolutionary investment in a surfeit of luxury function in these particular pathways or an inherent resistance to inflammatory demyelination, perhaps by virtue of predominant axonal size[187]is unclear. However, whilst single weakness or ataxic relapses in our study did not appear to be associated with relevant impairment, multiple weakness or ataxic relapses were and the inability of these relapses to affect mobility and in turn EDSS disability in the large natural history studies is initially perplexing until one considers that these studies are describing a population and not individual effect. Such multiple weakness or ataxic relapses in the same limb were an unusual phenomenon in our study: 18.8% of limbs had had multiple weakness relapses whilst only 6.7% of all limbs had had multiple ataxic relapses (see table 4-

2). A non or single relapsed limb is much more likely. In addition whilst most of these multiple relapses will be affecting the legs a significant minority will be affecting the arms (see chapter 3, figure 3-7a) which will have little affect on mobility and by the time arm function regains significant traction on the EDSS scale (EDSS score of 8 and above) it is highly likely that the secondary progressive phase will have supervened in any case. Thus it seems that multiple weakness or ataxic relapses coalescing in the same leg, whilst likely to be disabling to the individual, is sufficiently uncommon at the population level so as to allow any such disabling effect to be obscured in a morass of sensory, visual, mono-relapse weakness or ataxia, leg sparing relapse and EDSS idiosyncrasy before being completely lost in a tidal wave of secondary progression.

But what of the possibility that "Secondary progressive multiple sclerosis tends to affect whichever system has borne the brunt of the disease earlier in the course"[7]. There are in fact several reasons to suggest that the secondary progressive stage is independent of precedent relapse and our study supports and expands on such observations. Firstly in primary progressive disease there are often no relapses and therefore no dependence upon precedent relapses and the clinical character of disability and impairment is very similar to that of secondary progressive disease (see chapter 2). Secondly previously published work suggests independence of relapse and progression. In neuromyelitis optica where the relapses are generally more severe than in multiple sclerosis, secondary progressive transformation occurs much less frequently than in multiple sclerosis[188]. In 1949 Muller found that despite the heterogeneous nature of the relapsing disease phase the progressive disease phase was almost invariably characterised by motor disturbance[159]. However, it seems the prevailing scientific climate in 1949 was not conducive to Muller over emphasising his findings. Much more recently the London, Ontario group reported that the site of relapse and subsequent progression are largely unrelated[173]. This group examined single-attack progressive patients and found that whilst the site of relapse was heterogeneous, the site of progression was relatively stereotyped and appeared to have a predilection for the distal corticospinal tract. However whilst largely prospective methodology was employed, the attempt at localisation in this study was arguably less precise than our own and recorded only the neurological systems involved at onset and progression rather than localising them to a particular limb or

eye. Our study found that the presence of the secondary progressive phase was significantly associated with impairment across all 4 functional systems examined (see table 4-3) and that this association was independent of relevant relapse activity. Thus both relapses and progression are independently associated with chronic impairment but the relative resistance of motor pathways to relapse and their relative susceptibility to progression[159;173]forms a basis for explaining the disparate effects of relapse on disability reported by natural history studies[6;10;22] and shorter term studies biased towards the earlier disease course reporting a recordable effect of relapse on EDSS[30].

Thus we have shown that relapse is independently associated with relevant chronic impairment although motor pathways may be relatively preserved. We have also shown that the secondary progressive phase is independently associated with impairment in motor, cerebellar, sensory and visual pathways. We have also offered explanation as to why this is in fact entirely concordant with the large natural history studies of multiple sclerosis. But how might these findings be relevant to clinical practice?

Firstly it may suggest that targeting of the presently available disease modifying drugs towards those patients who are at risk of relapse related disability is feasible. The Association of British Neurologists has recently updated their guidelines for prescription of Beta-interferon and glatiramer acetate. The new guidelines (March 2007) now allow prescription of these drugs in CIS (clinically isolated syndromes) where McDonald MRI criteria for diagnosis of MS is met[15] as well as expanding the starting criteria and loosening the stopping criteria in established disease. These new guidelines broadly align UK practice with current European and United States practice which gives high regard to MRI monitoring of disease activity, despite the weak association between MRI activity and disability, and has confidence in the ability of these drugs to prevent long term disability despite a paucity of presently available evidence[189]. In an environment of imperative rationalisation our data begin to suggest a rationale basis for use of the disease modifying drugs that may be less ambiguous than existing guidelines that include terms such as 'clinically significant' and 'disabling' relapse. If the desired outcome is to prevent disability as measured by the EDSS it would seem sensible, based on our data, to aggressively target any

weakness or ataxic relapse, particularly involving the legs after only a single attack. The rationale being that it is not the first such relapse that is associated with chronic impairment but the second or subsequent relapses. Although our data does not include any CIS patients meeting McDonald criteria it would seem reasonable to consider treating these patients providing the CIS involved weakness or ataxia. Based on our data in isolation treating sensory relapses or optic neuritis would be less likely to have a long-term benefit on disability although our data suggest that their prevention may reduce relevant impairment – and indeed this has been reported in a trial of Natalizumab[190]with regards to visual acuity.

Secondly our data highlight the critical importance of choice of outcome measure[21]. This is already suggested by studies comparing various outcome measures that show poor longitudinal correlations in responsiveness over time[191;192]. Our study indicates that the multiple sclerosis relapse/progression paradox may at least partly be an artefact of imperfections in the EDSS. It is unlikely that any disability scale will ever be perfect but we need to recognise such imperfections when evaluating both natural history and therapeutic data to ensure we are recognising disease, and not scale, related phenomena. The mobility segment of the EDSS scale appears largely insensitive to the effect of relapse and we have highlighted possible reasons for this. Newer and probably more robust and sensitive disability scales may be found to be more sensitive to relapse related impairment and in turn give relatively favourable outcome data for the disease (relapse) modifying drugs - but this doesn't mean that the EDSS data are wrong or that newer outcomes are necessarily any more worthwhile. Partly it is a question of our own intuitive definition of disability and the EDSS, despite its inherent peculiarities, possibly reflects this quite well.

Thirdly we have shown the importance of considering relapse quality in both natural history and therapeutic research in multiple sclerosis. In a condition such as multiple sclerosis where the underlying cause and effect are debated it seems appropriate to give precise consideration to the quality and location of the individual components of this argument. If the inflammatory component of this disease were the cause of the degenerative component of this disease then one would expect to see both sharing a very similar character separated in only in time but not space. Maintaining the chain of possible cause and effect in natural history studies requires localisation of both

relapse and progression. We believe that a prospective attempt to do this involving similar or greater detail in localisation than we have demonstrated would help further answer these questions and such techniques may become useful in therapeutic trials – even possibly allowing shorter trials with fewer patients but using focused 'cause and effect' clinical outcomes without the heavy reliance on arguably questionable MRI surrogates.

Chapter 5: Plasma exchange in episodes of severe inflammatory demyelination of the central nervous system

Introduction

Severe acute inflammatory demyelination of the central nervous system (CNS) can occur in multiple sclerosis (MS), including the Marburg variant[193], acute disseminated encephalomyelitis (ADEM), acute transverse myelitis and neuromyelitis optica. All of these conditions commonly respond to intravenous corticosteroids. With the exception of MS, they are infrequent disorders, and in MS individual episodes of inflammatory demyelination are often not severe and, moreover, are usually steroid responsive and followed by good clinical recovery in the short term[194]. Therefore severe acute inflammatory demyelination of the CNS that does not respond well to intravenous corticosteroids is rare and large treatment trials have not been done. Consequently there is still doubt as to the best management of this condition.

Early studies of plasma exchange for inflammatory demyelination concentrated on its possible role as a treatment for chronic progressive MS. Some studies suggested a benefit[195-198], but they were often confounded by concurrent immunosuppressant usage. Others did not demonstrate a benefit[199-202] including two randomised, blinded, sham controlled studies[199;200]. However reports on the value of plasma exchange for severe, acute MS relapses that are resistant to steroid therapy[203-205] have been more promising. Similarly case reports of successful use of plasma exchange in other episodes of severe, inflammatory demyelinating CNS disease, including acute disseminated encephalomyelitis (ADEM)[206-208] and Devic's syndrome[209] suggest that plasma exchange could be useful across the full spectrum of severe acute inflammatory demyelinating CNS disease.

A sham controlled double blind randomised crossover trial of plasma exchange in 22 adult patients with acute central nervous system inflammatory demyelinating disease who had not responded to corticosteroid therapy[210] found moderate or greater

neurological improvement occurred in 42.1% of patients receiving plasma exchange (7 exchanges over 14 days) compared with 5.9% in the sham exchange group (p=0.011). A subsequent report[211] of the effects of plasma exchange in 59 cases, including the 22 patients involved in the aforementioned trial[210], has continued to support its use in acute severe inflammatory CNS demyelination. Both of these studies[210;211] that support the use of plasma exchange specifically in acute severe demyelination of the CNS issue from the same centre (the Mayo clinic).

In this chapter we describe six consecutive patients with acute severe inflammatory CNS demyelination who failed intravenous corticosteroid therapy and were treated with plasma exchange.

Methods

From 2001 to 2003, a total of 6 adult patients with severe acute steroid-insensitive inflammatory demyelinating CNS disease have undergone plasma exchange at the National Blood Service Apheresis Unit in Bristol. This chapter summarises the results and progress of all six patients. These are the only patients we have treated with plasma exchange for severe acute steroid-insensitive inflammatory demyelinating CNS disease at this centre.

For inclusion into this retrospective analysis patients were at least 16 years old at the time of plasma exchange, had a clinically and radiologically secure diagnosis of severe acute inflammatory CNS demyelination and other therapeutic options – which always included intravenous methylprednisolone (1g daily for at least 3 days) - had proven unsatisfactory. Plasma exchange was performed using Gambro-BCT ® Spectra TM apheresis machines. A single plasma volume exchange was performed on each occasion. Each individual patient's plasma volume was calculated by the program software based upon patient height, weight, gender and haematocrit. Human albumin solution and saline were used as replacement fluids and citrate as anticoagulant.

To assess the significance of plasma exchange on estimated Expanded Disability Status Score (EDSS) and relapse rate in the surrounding year we applied the sign test, as the datasets were small and non-parametric.

Case Reports

Patient 1

A 35 year old male presented with a rapidly progressive spastic paraparesis with a sensory level at T4. Blood examination was unremarkable. Cerebrospinal fluid examination revealed normal opening pressure, protein, glucose, negative oligoclonal bands, 5 lymphocytes and 70 red cells per mm^3. Brain MRI was normal but MRI of the spinal cord revealed swelling, with T_2 hyperintensity and some gadolinium enhancement from C6/7 to T2. Biopsy of the MRI denoted cord lesion revealed acutely reactive and oedematous spinal cord white matter. There was comparable loss of axons and myelin, prominent microglial activation but no macrophages and very few lymphocytes. There was no evidence of infection, granulomatous reaction, tumour or vasculitis. A diagnosis of acute transverse myelitis was made.

Clinically he rapidly lost all power in his legs despite two courses of intravenous methyl-prednisolone. He was stable for 3 months before slowly recovering some movement and sensation in his legs but remaining wheelchair dependent. After a further 2 months his myelitis extended proximally and he developed weakness and numbness in his arms that again proved refractory to intravenous steroids. He received a course of 5 plasma exchanges. Following the first plasma exchange he reported an improvement in his arms and following the second plasma exchange the improvement was noted objectively. He also noted an increased rate of improvement in his legs. Five months later he had near-normal function in his arms and walks with a pair of crutches.

Patient 2

A 35 year old Chinese male presented with a 1 day history of bilateral blurred vision and weak legs. Neurological examination revealed an asymmetrical spastic paraparesis with a sensory level at T8. Routine blood tests and chest X ray were normal. Brain MRI revealed multiple T2 hyperintense lesions involving both cerebral hemispheres, the internal capsule, corpus callosum, basal ganglia, brainstem and cerebral hemispheres. Spinal MRI revealed three T2 hyperintense lesions in the cord at C7, T1-7 and T11 respectively. Cerebrospinal fluid was normal apart from a raised protein of 0.74g/dl. No intrathecal synthesis of immunoglobulin was detected.

The patient was initially treated with intravenous methylprednisolone 1gram daily for 3 days. His leg weakness was unaffected by the methylprednisolone. His vision improved during the course of methylprednisolone but deteriorated 2 days after the last dose and within a week his visual acuity was only sufficient for finger counting in either eye. His deteriorating vision at this stage was accompanied by new neurological deficits including diplopia, right arm weakness, urinary retention and worsening paraparesis such that he was only able to mobilise slowly with the aid of a walking frame. A further 3 day course of intravenous methylprednisolone was temporally associated with an objective improvement in limb power and visual acuity. 2 days after finishing this course of methylprednisolone the patient's limb strength deteriorated and was followed by deteriorating vision such that within 6 days of finishing steroids he was finger counting only in either eye and walking slowly with a wheeled frame.

The patient had a course of 5 plasma exchanges over the following 10 days. An improvement in limb strength was objectively noted within a day of the first plasma exchange and improved visual acuity was demonstrated the following day. On the day of the final exchange he had a steady gait without any support and his visual acuities improved to 6/6 and 6/12 in the right and left eyes respectively. His visual acuities relative to his treatment can be seen in Chart 1. He was discharged home at this point. At follow up 6 months later he was found to be well and normally mobile

whilst his vision was reported as satisfactory. Neurological examination at this stage was normal apart from pale optic discs.

Patient 3

A 41 year old female with a 3 year history of aggressive progressive multiple sclerosis with continuing superimposed relapses presented with rapidly accumulating disability. Her diagnosis had been made on the basis of the clinical presentation, a typical MRI brain scan, positive oligoclonal bands, delayed visual evoked potentials and absence of confounding results.

In the 3 years preceding the use of plasma exchange she experienced progressive accumulation of disability and had required 5 courses of intravenous methylprednisolone (1g/day for 3 days) for 5 separate relapses, each with sub-optimal response. Because of her progressing disability, frequent relapses and perceived lack of response to intravenous steroids a course of intravenous mitoxantrone (12mg/m^2 every 4 months) was started fourteen months prior to the first plasma exchange. The evidence for this dosing regime is from a study[212] that used 12mg/m^2 every 3 months but to allow the patient to recover from inter-dose relapses we were only able to achieve this dose every 4 months. Mitoxantrone was stopped after the 3rd dose and considered a treatment failure for the following reasons: (1) no clinical improvement had been noted at any stage during the course, (2) the patient had suffered a clinically significant relapse within 6 weeks of each of the three doses of mitoxantrone, (3) the patient was poorly tolerant of the mouth ulceration that followed each course, (4) the patient's disability continued to progress during the course of mitoxantrone such that following the third dose she had poor vision, a painful asymmetrical spastic tetraparesis, marked ataxia and vertigo. Her gait deteriorated markedly over the next 3 months such that she was unable to walk without a wheeled frame. In view of her previous treatment failures and her rapid disability progression she received a course of 5 plasma exchanges over 8 days. Immediately following her final plasma exchange limited but definite objective improvement in her gait was observed; her vertigo and pain however remained unimproved. In the 19 months of follow up she has had only one definite relapse (left

sided deafness), and her gait has remained stable although her vertigo and pain have deteriorated.

Patient 4

A 26 year old lady with a history of 'neurotic depression' presented with an acute onset of tetraparesis, more marked in the legs than arms and diplopia. Neurological examination revealed impaired upgaze in her left eye and partial tetraparesis and sensory loss in face and body but with normal tone, reflexes and flexor plantar responses. A CT scan of her head at this stage was normal. Routine bloods including inflammatory markers were normal. The patient showed spontaneous improvement and was discharged with no definite diagnosis. Six weeks later she was readmitted with worsening right sided limb weakness, diplopia, nausea and vomiting. Neurological examination at this stage revealed very hesitant speech, an inability to look to the right and a right hemiparesis with associated brisk tendon reflexes more marked in the arm than leg. Plantar reflexes remained flexor. Routine blood tests were again normal. Brain MRI revealed multiple T2 hyperintense lesions mostly in the white matter of the upper hemispheres, many of which were in the corona radiata and close to the ventricles. Lesions were also present in the medial temporal lobes and in the left cerebellar hemisphere. CSF examination revealed oligoclonal bands and negative herpes PCR. The patient was treated with intravenous methylprednisolone 1 g/day for 5 days followed by a 7 week tapering course of oral prednisolone. The patient actually deteriorated during the course of intravenous steroids: she developed visual disturbance on the first day of the course and was noted to have visual acuities of 6/9 in both eyes. On the final day of intravenous steroid administration her acuities had deteriorated to 6/36 in the right eye and she had lost light perception in the left eye. Slow improvement in vision and right hemiparesis coincided with the commencement of the oral prednisolone tapering course such that after 2 weeks of oral steroids the patient was reliant on a walking frame for mobility and visual acuities were 6/12 and 6/24 in the right and left eye respectively.

Over the next 13 months she was admitted to hospital on 6 separate occasions for a total of 126 days. Three of these were 'emergency' admissions for disabling relapse

whilst the remaining 3 admissions were on an elective basis for administration of intravenous immunoglobulin for recent relapse. In total during this period she had 2 courses of intravenous methylprednisolone (1g per day for 3 days) with tapering oral prednisolone to a lowest dose of 7.5mg per day, 4 courses of intravenous immunoglobulin (0.4mg/kg/day for 5 days) and was commenced on azathioprine 150mg per day. There was sub-optimal improvement with the steroid courses and improvement that lasted less than 1 month following each course of intravenous immunoglobulin.

The last of these admissions was for a further disabling clinical relapse that left her requiring the support of 2 people to walk where previously she had been mobile with a walking frame. Following an ineffective course of intravenous methylprednisolone she received a course of 5 plasma exchanges over 13 days. On the day following the final exchange she was able to walk independently with a walking frame and after a further six weeks she was able to walk about 20 metres with 2 walking sticks. She has remained well for the twenty-four month follow up period and her walking has continued to improve such that 21 months after her course of plasma exchange she reports that she is able to walk a quarter of a mile with one stick. She has had no relapses during this period.

Patient 5

An asymptomatic 16 year old male attended his opticians for routine review of his short sightedness and a non correctable deterioration in his vision was noted. He was referred to an ophthalmologist who noted corrected acuities of 6/9 in both eyes with normal fundoscopy and a 'subtle eye movement disorder'. Over the following three months the patient developed headaches, blurred vision, a clumsy gait with occasional falls and a tendency to drop things. An MRI brain scan at this stage showed multiple T2 hyperintensities within the cerebral white matter, most marked within the periventricular white matter, anterior temporal lobes, pons and medulla. CSF examination revealed oligoclonal bands. Further blood investigations were unremarkable and a diagnosis of multiple sclerosis was made. His ataxia responded well to a three day course of intravenous methylprednisolone. However four weeks

after the course of steroids his disease continued to progress. His neurological deterioration subsequently accelerated rapidly such that ten months after his first symptom he had become dependent upon a wheeled frame to take just a few steps. Neurological examination at this stage revealed a partial left internuclear ophthalmoplegia, a spastic paraparesis and cerebellar ataxia.

In view of his rapidly accumulating disability and young age a course of plasma exchange was instituted. He received 5 plasma exchanges over a 2 week period. By the end of the course was able to walk 15 metres without support. In the 14 months since his plasma exchanges he has progressively improved, despite suffering 3 superimposed relapses (1 episode of ataxia, 2 episodes of right optic neuritis), such that at the end of his follow up period he is able to walk 500 metres without any support.

Patient 6

A 17 year old male presented with slowly progressive personality change, seizure disorder, cognitive decline, intermittent episodes of optic neuritis and gait disturbance. Full neurological investigation revealed a diagnosis of multiple sclerosis based on the clinical history, typical MRI brain appearances, positive oligoclonal bands, delayed visual evoked potentials and lack of confounding results. He improved following initial courses of intravenous methylprednisolone. Over the 3 years from presentation his disease course was progressive with 3 superimposed relapses. At this stage he was markedly ataxic and required the support of one carer to stand. Over the next 3 months he deteriorated rapidly despite a course of intravenous corticosteroids such that at the end of this time he was bed bound with quadriparesis, bulbar dysfunction and cognitive decline. A decision was taken to treat him using plasma exchange. Due to an MRSA colonisation of his central line he received only 3 of 5 planned exchanges. Following plasma exchange his family said he had improved. Clinically there was some improvement in cognitive function and speech but this was sub-optimal and the patient has remained quadriparetic and fully dependent. No relapses were recorded in the 12 months of follow up.

Results

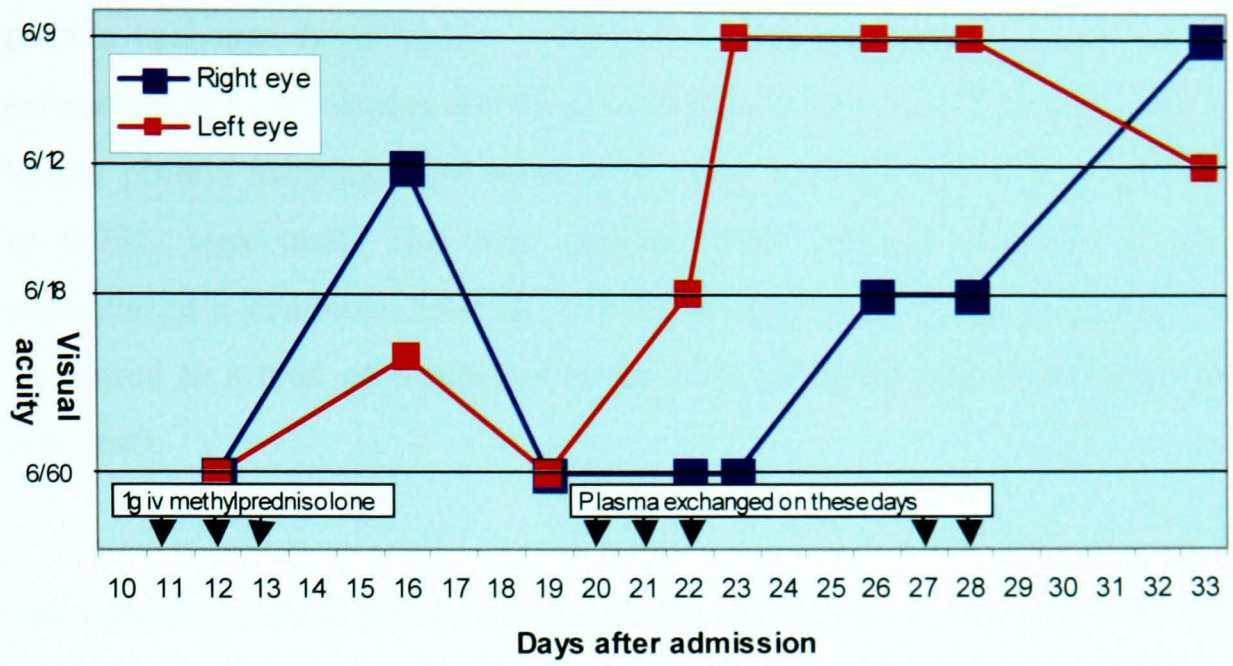
Table 5-1: Patient and disease characteristics

				Duration at PE (months)		
Patient number	Age (yrs)	Sex	Diagnosis	Disease	Acute episode	Major involvement
1	35	Male	Acute transverse myelitis	5	5	Quadriparesis
2	35	Male	Clinically isolated optico-spinal syndrome	1	1	Paraparesis
3	43	Female	Secondary progressive MS with relapses	34	3	Paraparesis
4	27	Female	Relapsing remitting MS	17	1	Paraparesis
5	17	Male	Relapsing remitting MS	10	1	Cerebellar
6	20	Male	Secondary progressive MS with relapses	45	4	Quadriparesis

Table 5-2: Treatment and Response

Patient number	Plasma exchanges		Time (days) from last iv steroids to PE	Estimated EDSS			Relapse rate (relapses/year)		Follow up (months)
	No.	Period (days)		Before	After	EDSS change	Year before PE	Year following PE	
1	5	11	38	8.5	6.5	-2	NA	NA	5
2	5	10	9	6.5	2	-4.5	NA	NA	6
3	5	8	176	6.5	5.5	-1	3	1	19
4	5	11	24	7.5	6.5	-1	3	0	24
5	4	8	114	7.5	4	-3.5	2	2	16
6	3	4	108	9.5	9	-0.5	2	0	12

Figure 5-1: Visual acuity of patient 2



A summary of the patient and disease characteristics is shown in Table 5-1, whilst the results of plasma exchange in these patients is shown in Table 5-2. There were 4 men and 2 women. Age at time of plasma exchange ranged from 16 to 41 years (mean 29.5 years). Four of the patients were suffering from multiple sclerosis with a disease duration of between 10 and 45 months (mean 26.5 months) whilst there was one case of acute transverse myelitis and one case of clinically isolated optico-spinal demyelination. The follow up period averaged 13.7 months and ranged from 5 to 24 months.

Of the six acute episodes that led to a course of plasma exchange five principally involved probable spinal cord lesions whilst one episode principally involved cerebellar dysfunction. The number of plasma exchanges given to each patient ranged from 3 to 5 (mean 4.5) and were given over 4 to 11 days (mean 8.7). Four of the patients had a sub-optimal response to at least one course of intravenous methylprednisolone during the same admission where plasma exchange was administered. Two patients did not receive steroids during their admission for plasma exchange: in one of these cases (patient 3) this was due to a long history of unsuccessful steroid response and in another case (patient 5) this was due to rapidly accelerating neurological deterioration in a young patient whose previous favourable response to intravenous steroids had lasted for only 4 weeks. The time from

intravenous steroid course to plasma exchange ranged from 9 to 176 days (see table 5-2). Only patient 4 was receiving concurrent immunotherapy at the time of their plasma exchange (azathioprine 150mg/day). The case notes allowed retrospective estimation of EDSS scores and these ranged from between 6.5 and 9.5 (median 7.5) before plasma exchange and between 2 and 9 (median 5.5) after plasma exchange ($p=0.031$, sign test). The four patients with multiple sclerosis in the study experienced a combined total of 10 relapses in the year prior to plasma exchange compared to a total of 3 relapses in the year following plasma exchange ($p=0.25$, sign test).

Our complications of plasma exchange were as follows. All patients required central venous access despite an initial attempt to complete the course of plasma exchange via peripheral access in two patients. Two patients developed an infection of their central venous (CV) line, both cases responded well to CV line removal and antibiotic therapy. One patient had their planned course of plasma exchange curtailed due to CV line infection. One patient required their CV line to be replaced due to poor line patency. One patient reported light-headedness for a few hours following each plasma exchange. No patient developed anaemia or systemic infection.

Discussion

This study although retrospective and uncontrolled, nevertheless provides further clinical support for the value of plasma exchange in steroid resistant acute severe inflammatory demyelination of the central nervous system. The 6 patients described had received a total of 9 courses of intravenous methylprednisolone in the 6 months prior to plasma exchange; two had also been treated with intravenous immunoglobulin and with mitoxantrone respectively without objective benefit. Although the extent of the response varied, all improved following plasma exchange. The possibility that improvement in some patients was at least partially a delayed effect of intravenous corticosteroid therapy cannot be excluded, though since the mean period between last steroid dose and plasma exchange was over 78 days, this seems unlikely. None of our patients had the number of plasma exchanges (seven) given in the Mayo[210] study, perhaps suggesting that fewer than seven plasma exchanges may be efficacious. Further research is required to clarify this issue.

Acute relapses in MS are thought to be inflammatory in origin, progressive disability the result of accumulating axon loss. The mechanisms of action of plasma exchange remain obscure[213], but are far more likely to affect immunological and inflammatory processes than neurodegeneration. Many neurological diseases are indeed characterised by the presence of a specific auto-antibody: Myasthenia Gravis, Lambert-Eaton Myasthenic syndrome, Stiff Person Syndrome and Miller-Fisher syndrome to name but a few. In MS however a single specific auto-antibody has yet to be described and given the relative abundance of MS and the quantity of research into MS when compared to the often much rarer conditions outlined above one must doubt whether such an entity exists. Antibodies against myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) have been described in MS but are limited to sub-groups only[214] and it is unclear whether they are causative or reactive.

The responses exhibited by our patients usefully illustrate these various aspects of the activity of plasma exchange. Patients 3 and 6, for example, both suffered an inexorable gradual deterioration over a 3 month period prior to their plasma exchanges. Clinically it was difficult to exclude aggressive, subacute relapsing

disease (rather than secondary progression), hence the trial of plasma exchange. The favourable response of Patient 3 supports inflammation rather than neurodegeneration as the basis for her deterioration. The relatively poor outcome of Patient 6 may imply irreversible axonal loss and secondary progressive disease had already commenced. The occasional difficulty, illustrated by these two patients, of clinically distinguishing between sub-acute frequent relapses and secondary progression, together with the clinicians desire to offer severely affected patients every possible therapeutic support, may on a larger scale help to explain the variable and ultimately inconclusive outcome of studies[195-202] examining the role of plasma exchange in progressive multiple sclerosis.

Within the group of patients with more unambiguous inflammatory action, our results help suggest two separate actions of plasma exchange: the immediate suppression of acute inflammation, and longer term prevention of further inflammatory relapses. Previously published trials[210;211] have concentrated more on the former, emphasising recovery from relapse, than the latter.

Thus, in our case of acute transverse myelitis (patient 1) a complete spastic paraparesis began to ascend after several months and threatened a tetraparesis. Plasma exchange in this case was closely associated temporally with resolution of arm symptoms and rapidly accelerated improvement in the legs. The response to plasma exchange even at this very late stage suggests that neurological cord dysfunction was at least partly due to reversible conduction block[215] not irreversible axonal loss.

In our case of clinically isolated optico-spinal demyelination (patient 2) in a Chinese gentleman, which may in time prove to be the first relapse of an oriental phenotype MS[216], a significant improvement in vision followed each course of intravenous methylprednisolone but lasted only 1-2 days. Plasma exchange was followed by dramatic but also sustained improvement (see figure 5-1). This again suggests a role for reversible conduction block caused by agents sensitive to but not abolished by steroids.

Beyond the immediate effects on acute relapse, we noted in our four patients with multiple sclerosis a lower relapse rate following plasma exchange. Whilst further prospective, blinded and sham controlled studies are required to examine whether this tentative observation is valid, or either a result of sub-optimal trial design or merely regression to the mean in a population selected for high relapse rate it does at least suggest the possibility that the plasma exchange may not only promote recovery from acute relapse but also prospectively reduce further attacks for a period of time. Indeed of three studies[217-219] which have looked at the effects of plasma exchange on brain MRI gadolinium-enhancing lesions one found a reduction[217] in the number of gadolinium-enhancing lesions following PE; one found no change[218] and the other reports an increase[219]. It is therefore suggested that PE may modify the overall inflammatory process[219]. The mechanisms by which plasma exchange may bring about a sustained effect are not clear but previous observations of a beneficial effect of plasma exchange on cellular immunity [220] in addition to the immediate effects on humoral response in multiple sclerosis may be pertinent. In our and other studies, patients are selected by virtue of a very severe clinical relapse and a more aggressive and inflammatory MS phenotype: therefore the possible reduction in relapse rate may not be generalisable to all cases of relapsing remitting MS.

Subsequent to our study the importance of the four distinct immunopathological patterns of MS lesion[42] (see Chapter 1) with regard to response to plasma exchange has been described. In 19 MS patients in whom brain biopsy was performed prior to plasma exchange there was a strong correlation between favourable response and the presence of pattern II lesions (antibody and complement mediated) at biopsy[43]. Whilst biopsy was not performed in any of our 4 MS patients their generally favourable response may be more than pure fortune: pattern II lesions appear to be more common than the three other pattern types combined[42]. Whether with hindsight one would have performed brain biopsy prior to plasma exchange in these cases to assess whether pattern II lesions were present is also doubtful as the risks of brain biopsy probably exceed the risks of plasma exchange, especially when there is little or no doubt about the diagnosis of MS based on clinical and para-clinical parameters.

Our findings from chapter 4 suggest that recurrent motor relapses isolated in CNS space do cause relevant chronic impairment and it is likely that such motor impairment would translate effectively into chronic disability. However such recurrent motor relapse activity is relatively uncommon and is likely to be a significant cause of disability in only a minority of patients, however it is these very patients in whom we would tend to consider more aggressive anti-inflammatory therapies, such as plasma exchange, and our work suggests this is appropriate. The finding that motor relapses probably do contribute to chronic disability is supported by a trial of the humanised monoclonal antibody Campath 1-H which suppressed relapses in patients with relapsing remitting disease and led to an improvement in disability. It was suggested that suppression of the inflammatory environment protects axons from secondary degeneration which can cause disability[109], although our own observations suggest that relapse suppression alone in the case of aggressive relapsing motor disease would probably be enough to ameliorate disability independent of any action on secondary progressive disease and this is highlighted further by the observation that effective suppression of relapse and MRI surrogates by Campath-1H in those with secondary progression did not halt progression of disability or CNS atrophy[12].

The complications our six patients experienced from plasma exchange, whilst fortunately not resulting in lasting morbidity, highlight that it is not to be undertaken lightly or until less risky interventions such as intravenous methylprednisolone have been exhausted.

Our study supports the use of plasma exchange in cases of severe acute steroid-insensitive inflammatory demyelination of the CNS.

Chapter 6: Conclusions

What has this work contributed to our understanding of multiple sclerosis?

Whilst multiple sclerosis undoubtedly involves inflammatory demyelination in the central nervous system of humans there is an emerging controversy as to whether this is a primary or secondary disease phenomenon. Does inflammation cause neurodegeneration or does neurodegeneration cause inflammation? The latter possibility represents a potential paradigm shift in multiple sclerosis theory[221;222]. Early clinical and pathological studies of multiple sclerosis gave rise to the intuitively attractive primary inflammatory model driven by a Th1 lymphocyte dependent, macrophage mediated auto-immune response directed against myelin derived antigen. However, subsequent therapeutic, radiological, clinical and pathological studies have arguably done more to question than support the primary inflammatory model. The key cornerstones of this debate include clinical, MRI and pathological information.

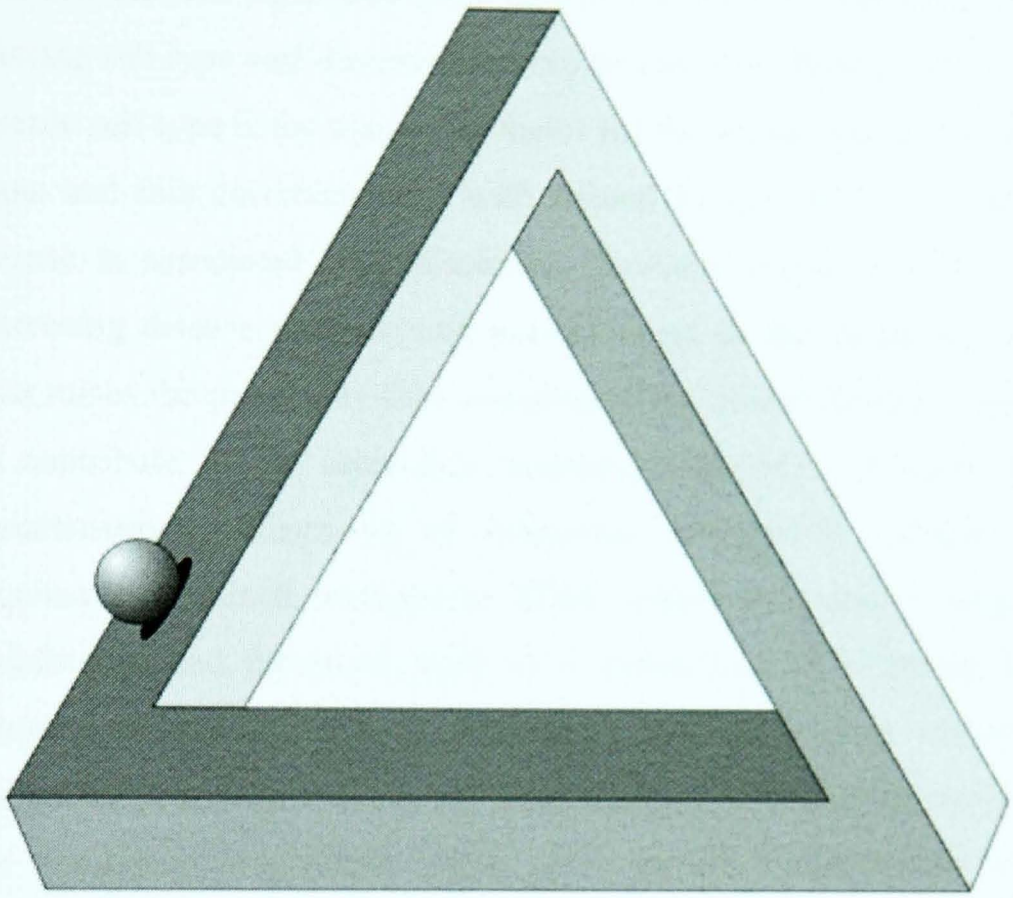
Whilst the ***pathology*** *is the disease,* access to the most revealing early disease stages is limited. Thus potentially critical observations of oligodendrocyte apoptosis preceding inflammation in the earliest stages of the disease[3] should be tempered by the knowledge that severe disease necessitating biopsy or facilitating post mortem pathology is unusual and it is difficult to be sure that this is representative of the more abundant, milder disease forms where tissue from early stage disease is ethically unobtainable. For this reason there has been a great interest in non-invasive neuro-imaging, principally magnetic resonance imaging.

Whilst **MRI** rapidly established a role in the diagnosis of multiple sclerosis[15], the technique was less proficient in terms of prognosis: there is a relatively poor correlation between conventional MRI indices and disability[69;223]. Subsequent studies have shown a profound effect of disease modifying drugs on conventional MRI indices[107] but this translated into a weaker effect on relapse rates and no discernible effect on disease progression[12]. At this stage multiple sclerosis was perhaps telling us rather more about MRI than MRI was about multiple sclerosis and this was realized

when subsequent studies of the much less visually captivating 'normal appearing' white and grey matter revealed that these tissues are far from normal[39-41;49;53;54;80;82;83;85;86;88;91;93;224-226]. This raised the possibility that the 'multiple scleroses' are the equivalent of the cherry on the hitherto invisible cake. Additional evidence for the growing discrepancy in the primary inflammatory model included natural history data suggesting a fundamental dissociation between relapse and chronic disability[6;10;11;23;120;173] and the realization that the 'immune system' is not bound by any job description and is more a 'cell based survival system' that may have evolved a potent neuro-protective and regenerative capacity[26;227] within the now massive and latterly long lived human brain.

Paradox abounds: relapses correlate poorly with chronic disability[120;138], conventional MRI indices correlate poorly with disability[223], pathological features can not be accurately determined with conventional MRI indices[81] and obvious pathological change may not be clinically eloquent[67]. Thus the relationship between clinical, radiological and pathological features of multiple sclerosis appears tortuous at best (see figure 6-1).

Figure 6-1: M.C. Esher's Penrose Triangle figuratively illustrates the paradoxical relationship between clinical, radiological and pathological features of multiple sclerosis



The debate over the primary cause of multiple sclerosis continues without satisfactory resolution[228;229]. In this new cognitive climate of pathogenic uncertainty we believed that a return to the study of the living patient with the traditional tools of the neurologist, which was so much in evidence prior to, but increasingly scarce since the advent of MRI, may reveal information useful in advancing our understanding of multiple sclerosis.

The reader will recall that the **aims** of this thesis were as follows:

1. **To describe the relationship between relapse and disability in multiple sclerosis.**
2. **To describe the neurological deficits encountered during relapses of multiple sclerosis.**
3. **To describe in detail the neurological deficits at prevalence in a defined population of patients with multiple sclerosis.**

In **chapter 2** we have described in detail the neurological deficits at prevalence in 150 patients with multiple sclerosis. Furthermore we have examined the relationship between clinical signs and both patient related (sex and age) and disease related (disease sub type and disease duration) factors. Our findings show that a progressive disease sub-type is the major risk factor for the appearance of the majority of clinical signs and this correlates well with natural history data that find that progressive disease is associated with disability. However certain clinical signs appear with increasing disease duration and not the onset of the secondary progressive phase. This raises the possibility that neurological tracts and functions may degenerate and so contribute to the secondary progressive phase at different times rather than simultaneously. Diagnosis of secondary progressive multiple sclerosis usually requires a sustained increase in EDSS *within* its mobility range and so if non-mobility related functions, such as a disturbance of vibratory sensation were to progress before this time it is unlikely that the patient would be identified as secondary progressive. However when a tract with high influence on mobility enters the secondary progressive phase, such as the cortico-spinal tracts, a sustained increase in EDSS, and thus a label of secondary progressive multiple sclerosis is likely. In this way the important observation that the progressive phase is stereotyped and related to degeneration of the distal cortico-spinal tract[173] should be viewed in the knowledge that this may at least partially be an effect of the definitions used. It has previously been suggested[138] that the presence of certain clinical signs, such as the Babinski reflex, may indicate imminent conversion to the secondary progressive phase of the disease by noting sub-clinical damage to the cortico-spinal tracts. Our observations extend this: if varying tracts degenerate in a relatively predictable order in multiple sclerosis then the identification of clinical signs unrelated to the cortico-spinal tract may give even earlier warning of classical disease progression than is currently appreciated. The applications of such data in therapeutic studies, particularly where relapses are effectively suppressed, could be invaluable. Whilst our study with its cross sectional design has exposed this question a prospective study would be required to answer it.

In **chapter 3** we have described the neurological deficits encountered during relapse in our cohort and compared it with data from other studies. Whilst the task of

retrospective relapse assessment was performed rigorously we believe this is likely to represent the weakest link in our methodology and therefore a detailed presentation of these results, with appropriate comparison and discussion, was necessary. The assessment of clinical signs was performed prospectively and therefore, notwithstanding known problems of inter and intra-rater variability[230], less likely to be confounding. We found some useful and to our knowledge previously unreported data suggesting that motor and sensory relapses become increasingly common distally (face:arm:leg ratio of 1:5:10), whilst the character of relapses varies in the ratio of 1:3:5 for ataxia:motor:sensory in our study. Accepting the heterogeneous reporting techniques found in the literature with regards to relapses, we believe our own relapse data are comparable with previous studies and this suggests that rigorous retrospective relapse ascertainment, whilst unquestionably inferior to diligent prospective assessment, is satisfactory.

In **chapter 4** we have described the relationship between relapse and chronic disability in multiple sclerosis. We have shown that relapse is independently associated with relevant chronic impairment although in a manner that is in fact, we believe, consistent with natural history studies that suggest relapse number and rate are not associated with long term disability. The major explanation for this paradox is that whilst the human central nervous system appears to be relatively resistant to the chronic effects of motor relapse, the EDSS is heavily predicated upon motor impairment and thus relapses at the population level fail to translate into meaningful longterm disability. Our data also show that progressive disease states are associated with impairment and this impairment is independent of relapse activity. In addition the motor pathway's apparent partial resistance to relapse does not protect against progressive disease that in turn translates effectively into EDSS measured disability. Further reasons that may amplify the apparent paradox between relapse and disability include relapses from presently unidentified disease sub types with a relatively benign relapse character (ie sensory) being compared in a quantitative fashion with relapses from a less favourable (ie motor) phenotype. Thus relapses do appear to cause relevant *impairment,* and probably short term disability at lower EDSS levels[138], but not EDSS measured *disability* in the longer term.

In **chapter 5** we have reported on the role of plasma exchange in severe, acute, inflammatory, demyelinating disease, including our own experience with 6 patients, 4 of whom had multiple sclerosis[231]. We found a varying benefit throughout all 6 patients which supported previous work suggesting a potential role for plasma exchange in inflammatory, demyelinating disease[210]. These patients were largely selected for treatment with plasma exchange by virtue of unequivocally disabling steroid insensitive relapses. In combination with our work (Chapter 4) showing that repeated motor relapses coalescing in CNS space do indeed cause appropriate impairment this suggests that aggressive anti-inflammatory relapse therapy, if appropriately targeted to the relatively small subset of patients who are at risk of relapse related disability, is likely to have a significant long term beneficial effect on disability.

Thus we would argue that we have both met and exceeded our original thesis aims outlined in the introduction and re-iterated above. Our findings in conjunction with recent advances by other researchers allow us to speculate further on the nature of multiple sclerosis:

(1) Disability and impairment in multiple sclerosis

If the EDSS scale defines disability then disease progression is a dominant cause of disability in multiple sclerosis and this effect is independent of relapse activity. Relapses are associated with relevant impairment and at the early disease stages (where EDSS is an impairment scale) this probably explains and supports the idea that disability is accrued in a stepwise fashion[30]. However the impairment caused by relapses does not translate well into chronic disability because motor functions appear to have a relative resistance to the chronic effects of relapse and the mobility portion of the EDSS is relatively insensitive to non-motor impairment. In this way our work appears to resolve the conflicts between studies showing no effect of relapses on disability in the longer term[6;10;22;23] and a study showing residual disability following relapse in the shorter term at lower EDSS[30] (and thus impairment) levels. This may suggest that McAlpine's original schemata[116] (see figure 6-2a) is an oversimplification and that disability cannot be accurately expressed in only two dimensions. Our findings from chapter 2 and chapter 4 suggest that different neurological tracts may have their own susceptibilities to the different disease processes involved in multiple sclerosis and therefore an expansion of McAlpine's original schemata can be proposed (figure 6-2b).

Figure 6-2a: An illustrative version of McAlpine's original schemata

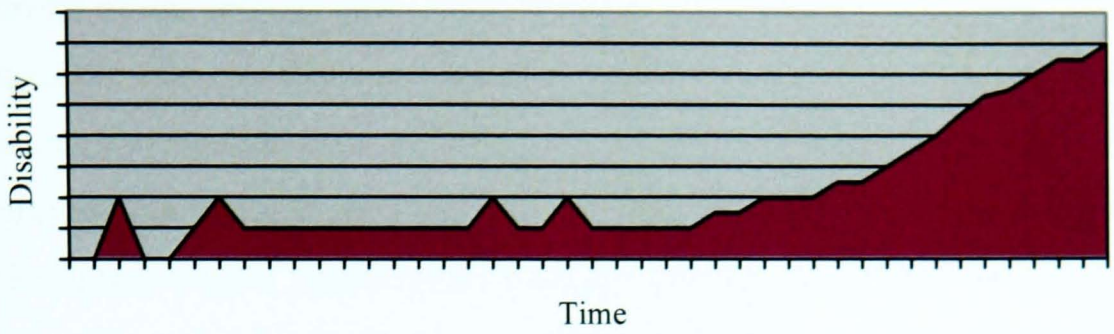
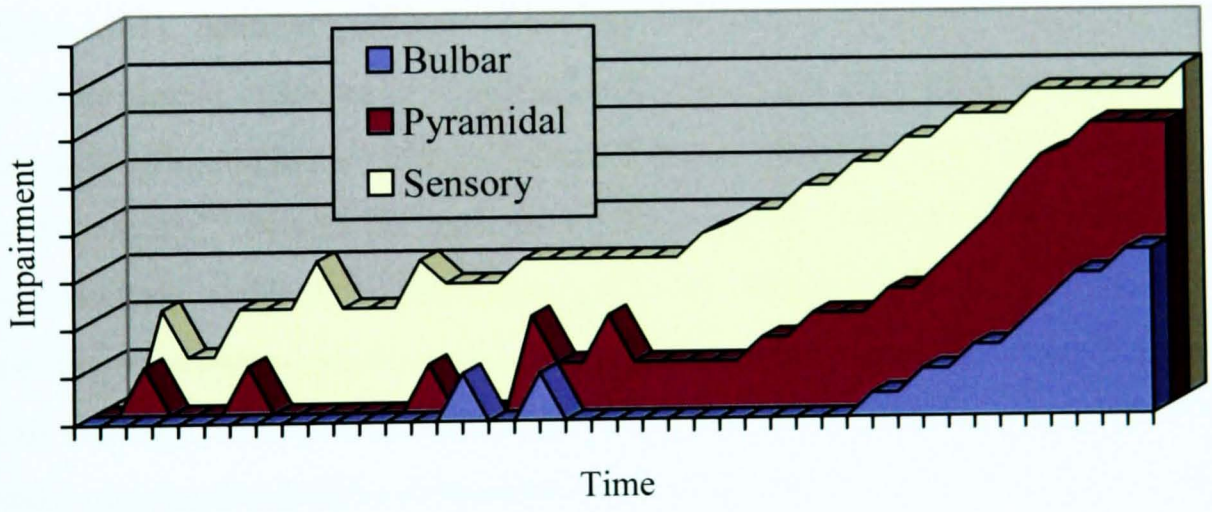


Figure 6-2b: An illustrative expansion of McAlpine's original schemata to take account of individual impairment in varying functional systems



The concept that there may be inherently different susceptibilities in varying central nervous system pathways to the many pathological processes involved in multiple sclerosis is supported by pathological studies[119;136;232]. One such study of the spinal cord[119] compared regional axonal density and tissue volumes at several levels of the spinal cord between the cortico-spinal and sensory pathways of patients with multiple sclerosis and healthy controls. Whilst, in common with previous work[232]

they found a significant reduction in cortico-spinal fibres at all spinal cord levels when compared with controls, this was only the case for sensory fibres in the upper levels of the cervical cord. Sensory fibres appeared to be better preserved in chronic multiple sclerosis than cortico-spinal fibres. This reflects clinical studies that suggest sensory symptoms are a relatively uncommon, or perhaps overlooked, component of progressive multiple sclerosis[159;167]. In addition an eloquent pathological study [187] of the anterior optic pathways in multiple sclerosis confirmed previous findings[136;233] suggesting that small diameter axons may be more susceptible to damage and loss than larger diameter axons. They found that there were significantly fewer small diameter axons (parvocellular) preserved in the anterior optic pathways of multiple sclerosis patients whilst there was relative preservation of large diameter axons (magnocellular). This observation corresponds with clinical experience: colour vision is mainly served by small diameter axons and is often affected early in multiple sclerosis. Surprisingly with regards to the sensori-motor system pathways we could find no information relating axonal size with function and found that others had encountered the same unanticipated information void (personal communication – Esiri MM). Another problem would be that axonal diameter in sensory pathways such as dorsal columns is compromised by the fact that these pathways contain a considerable number of efferent fibres. Efferent fibres are well described in optic[234] and auditory[235] nerves but their existence in spinal 'sensory' pathways is becoming increasingly realised[236]. Their function is not entirely clear but they may act as a peripheral sensory switch – you were likely unaware of the soles of your feet prior to this sentence. Any pathological study where the axonal diameter in certain pathways were measured would be compromised as one could never be sure whether each axon was technically going 'up' or 'down'. For these reasons we are presently unable to test the hypothesis that chronic impairment secondary to relapses is partially dependent upon the size of axons in particular CNS pathways but intuitively it remains an attractive theory. The fact that unmyelinated CNS axons may be as large as 0.8 micrometres in diameter whilst myelinated CNS fibres are often as small as 0.2 micrometres in diameter[237] further suggests that one needs to consider that patterns of axonal loss may appear to be demyelination dependent when they are in fact dependent upon axonal size.

(2) MRI in multiple sclerosis

Whilst our work did not involve the use of MRI limited inferences can be made with regard to use of this imaging modality. A major difference between an MRI and clinical study is the fact that MRI lesions are about ten times as common as episodes of acute clinical relapse. Our study suggests that these acutely eloquent MRI lesions are associated with relevant impairment in the fashion already described for relapses. The fact that correlations between T2 lesion load and disability are generally weak[69;223] may suggest that these acutely eloquent relapse associated lesions are the sole agents responsible for such a correlation. In turn this may infer that the clinically silent majority of MRI lesions remain clinically silent in the longer term and do not contribute towards chronic disability. This may help explain the comparatively greater effect of disease modifying drugs on MRI activity compared with relapse rates and their failure to provide unequivocal evidence of amelioration of chronic disability – they may be preferentially eliminating relatively benign or adaptive white matter lesions. This is further compounded by the fact that even in the heavily sclerosed central nervous system the majority of tissue is macroscopically normal appearing and so even a relatively subtle functional deficit in these normal appearing tissues may be more relevant to overall dysfunction and disability than a relatively marked deficit in lesional tissue.

The possible role of asymptomatic multiple sclerosis[64;67;68;238] is difficult to evaluate for obvious reasons of ascertainment but further support the dissociation between conventional MRI lesion loads and disability and suggest that therapeutically targeting MRI markers of disease in isolation may be ineffective and possibly harmful in individual cases. Is it possible that asymptomatic multiple sclerosis is a well-adapted response to an as yet unidentified primary pathology and that symptomatic multiple sclerosis represents a spectrum of failure at this attempt?

(3) A realistic alternative to inflammation as the primary pathology in multiple sclerosis?

Perhaps the most considered non-inflammatory primary mechanism in multiple sclerosis is oligodendrocyte apoptosis[3]. The triggering factor for this apoptosis is still

unclear, although possibilities include locally generated pro-inflammatory cytokines, oxidative and nitrative stress, excito-toxicity and persistent viral inflammation[239;240].Whilst there are many factors that need to be explained in any convincing model of multiple sclerosis it seems of at least some interest that multiple sclerosis only convincingly affects an organism that has recently evolved a massive cerebrum and an even more recent prolongation of life expectancy past the age at which multiple sclerosis usually starts. Evidently the oligodendrocyte has coped with humanity's increasing longevity and the presumptive mechanism is an increased oliogodendroglial life expectancy to exceed that of the host. However a significant number of human cell types cope with increasing host life expectancies not by increasing their own life expectancy but by a process of apoptosis and replacement by younger cells[241]. It has recently been realised that even human neurons have the ability to regenerate in adults[242] and so the possibility that oligodendrocytes employ this technique, not only exceptionally to repair obvious pathological damage, but also routinely to maintain a healthy, functioning, central nervous system over time is worthy of some consideration.

If this fundamental model of cycling rather than static oligodendrocyte cell populations were correct then a number of secondary (and necessarily even more tentative) observations can be made. Importantly a clear role for oligodendrocyte progenitor cells is immediately evident. It is unlikely that such cells would be there just in case the host were to develop multiple sclerosis and in any case they seem relatively ineffective when this is the case[243]. Such apoptosis and replacement of cells as large as oligodendrocytes would present its own difficulties. In particular concealing large amounts of apoptotic myelin from the attentions of the immune system would represent a technical challenge, and this task probably falls to endogenous microglia. The process of oligodendrocyte apoptosis would need to be carefully regulated to avoid microglia and oligodendrocyte progenitor cells becoming overwhelmed and thus prevent significant functional impairment of the nervous system during routine maintenance. Thus such oligodendrocyte apoptosis should be well dispersed in time and space and difficult to detect in pathological studies unless perhaps specifically looked for. If the useful lifespan of an oligodendrocyte is up to 20 –30 years then relatively few oligodendrocytes would need to be undergoing apoptosis at any given point in time. Dysregulation of oligodendrocyte apoptosis

may therefore explain at least some of the pathological[42] and even clinical expressions of multiple sclerosis. Failed diffuse apoptosis may lead to axons becoming slowly suffocated by functionally decrepit oligodendrocytes with partially adaptive venocentric focal apoptosis leading to the formation of the acute multiple sclerosis lesion[3], providing the opportunity for useful remyelination but also overwhelming the microglia and attracting T-lymphocyte and macrophage attention. Conversely a primary progressive phenotype may represent the same model without significant maladaptive focal apoptotic rescue mechanisms resulting in persisting axonal impairment[224] by dysfunctional oligodendrocytes and relatively less focal inflammation[72]: a study[233] of axonal loss in multiple sclerosis found that there was relatively little axonal damage in primary progressive disease suggesting that the degree of dysfunction in such disease is greater than can be explained on the basis of axon loss alone. We accept this proposed model is finely balanced on supposition with relatively few supporting facts, however it seems likely that any accurate model of multiple sclerosis would have to explain a lower than expected contribution towards disability from lesional matter and a higher than previously expected contribution from normal appearing white and grey matter[40;41;54;82;91;224].

Summary of Conclusions

- Relapses do cause relevant chronic impairment but for a number of disease and scale related reasons this fails to translate into chronic disability.
- Secondary progression is not dependent upon prior relevant relapse activity.
- Varying neurological functions and pathways may have varying susceptibilities and resistances to the different pathological components of multiple sclerosis.
- Many contemporary observations and paradox relating to multiple sclerosis may tell us as much about the tools used to make those observations, principally MRI and disability scales, as they do about the underlying disease.
- A model of multiple sclerosis based on a failure to maintain a physiological, dynamic oligidendrocyte population may have some merits.

Appendices

Appendix 1: Database Forms

Figure A-1: Patient Identification Data

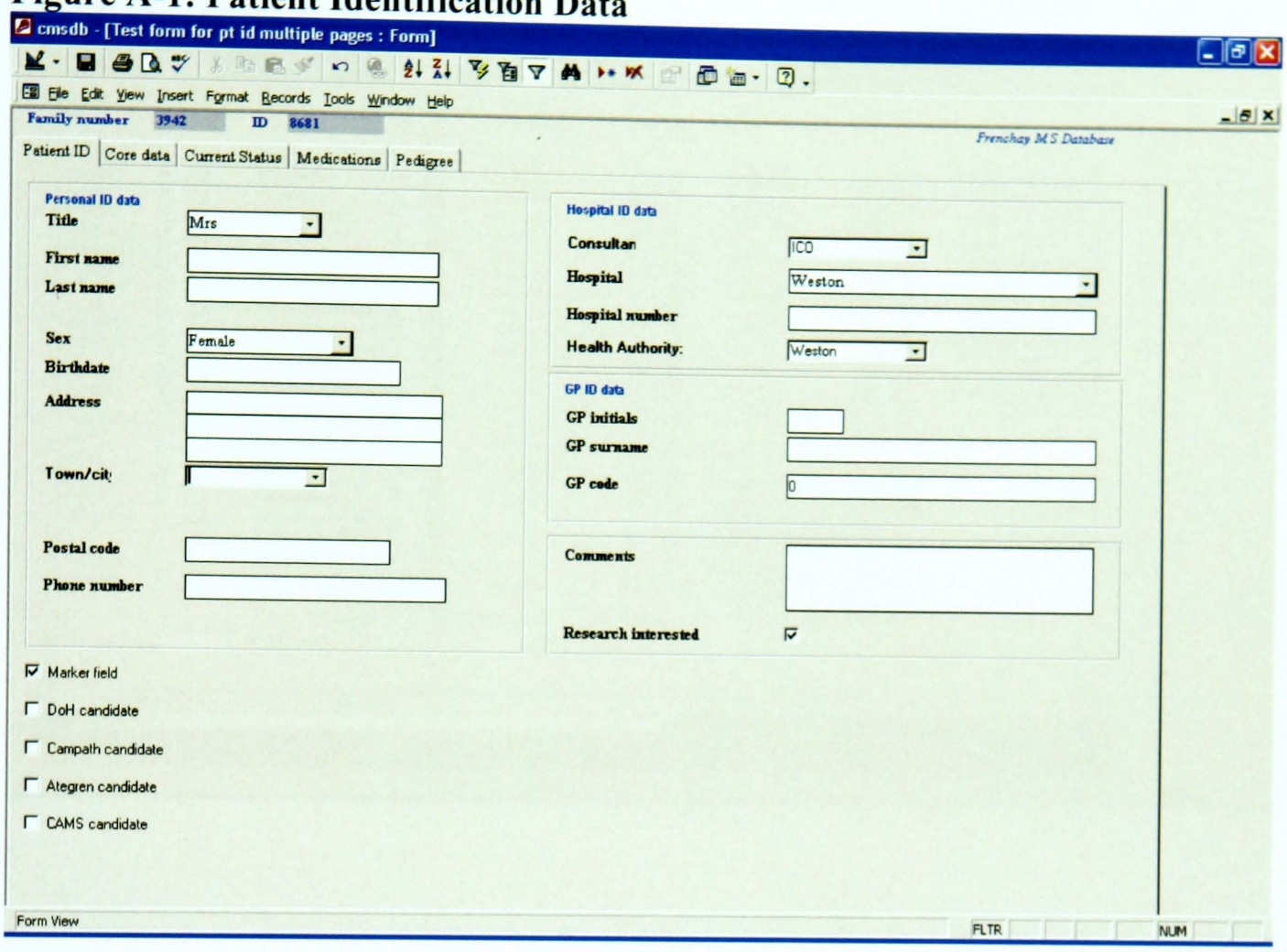


Figure A-2: Core and Relapse Data form

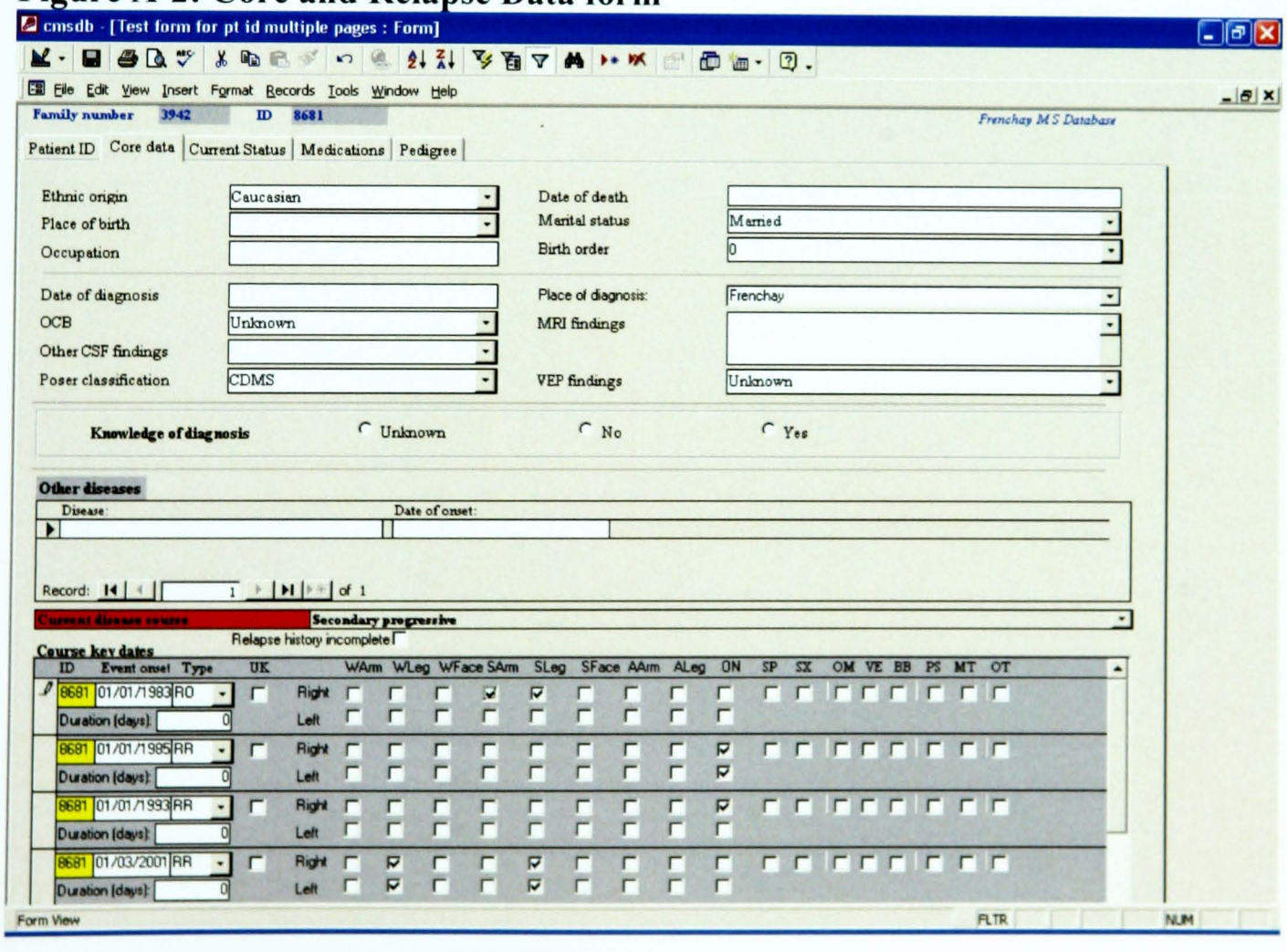
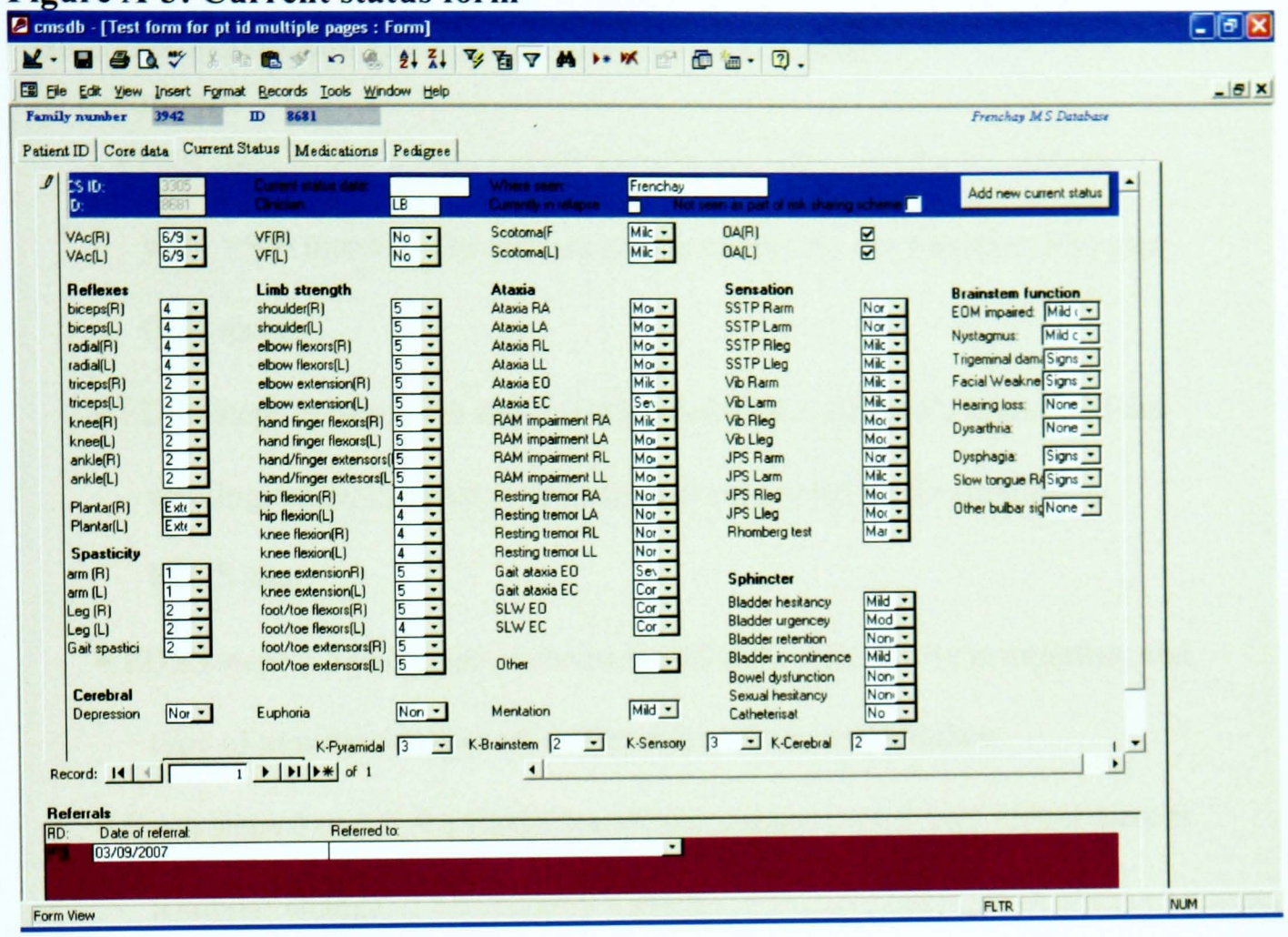


Figure A-3: Current status form



Appendix 2: Kurtzke's Expanded Disability Status Scale

(i) Definitions

- EDSS steps below 4 refer to patients who are fully ambulatory (able to walk >500 metres). The precise step is defined by the Functional System (FS) scores.
- EDSS steps between 4.0 and 5.0 are defined by both the FS scores and the walking range. In general, the more severe parameter determines the EDSS step.
- EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.
- From steps 0 to 4.0, the EDSS should not change by 1.0 step, unless there is a similar change in FS score by 1 grade.
- The EDSS step should not be lower than the score of any individual FS, with the expetion of the Visual and Bowel/Bladder FS.

(ii) Expanded Disability Status Scale

0 Normal neurological exam (all FS grade 0)

1.0 No disability, minimal signs in one FS (one FS grade 1)

1.5 No disability, minimal signs in more than one FS (more than one FS grade 1)

2.0 Minimal disability in one FS (one FS grade 2, others 0 or 1)

2.5 Minimal disability in two FS (two FS grade 2, others 0 or 1)

3.0 Moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four grade 2, others 0 or 1)

3.5 Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)

4.0 Ambulatory without aid or rest for >500 metres; up and about some 12 hours a day, characterised by relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades not exceeding limits of previous steps

4.5 Ambulatory without aid or rest for >300 metres; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combinations of lesser grades exceeding limits of previous steps

5.0 Ambulatory without aid or rest for >200 metres (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)

5.5 Ambulatory without aid or rest >100 metres

6.0 Unilateral assistance (cane or crutch) required to walk at least 100 metres with or without resting

6.5 Constant bilateral assistance (cane or crutches) required to walk at least 20 metres without resting

7.0 Unable to walk 5 metres even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day

7.5 Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and wheeling self

8.0 Essentially restricted to bed or chair or perambulated in wheelchair; but out of bed most of day; retains many self care functions; generally has effective use of arms

8.5 Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self care functions

9.0 Helpless bed patient; can communicate and eat

9.5 Totally helpless bed patient; unable to communicate effectively or eat/swallow

10 Death due to MS

Appendix 3: Functional System Scores

(i) Visual (Optic) Functions

Visual Acuity: The visual acuity score is based on the line in the Snellen chart at 20 feet (5 metres) for which the patient makes no more than one error (use best available correction). Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations.

Visual Fields

0 Normal

1 Signs only: deficits present only on formal (confrontational) testing

2 Moderate: Patient aware of deficit, but incomplete hemianopsia on examination

3 Marked: complete homonymous hemianopsia or equivalent

Scotoma

0 None

1 Small: detectable only on formal (confrontational) testing

2 Large: spontaneously reported by patient

Disc Pallor

0 Not present

1 Present

Note: When determining the EDSS step the Visual FS score is converted to a lower score as follows:

(Visual FS Score – Converted Visual FS score)

1-1, 2-2, 3-2, 4-3, 5-3, 6-4.

Visual FSS

0 Normal

1 Disc pallor and/or mild scotoma and/or visual acuity of worse eye less than 20/20 but better than 20/30

2 Worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59

3 Worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity of 20/60 to 20/99

4 Worse eye with marked decrease of fields and/or maximal visual acuity of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less

5 Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal visual acuity of better eye of 20/60 or less

6 Grade 5 plus maximal visual acuity of better eye of 20/60 or less

(ii) Brainstem Functions

Extraocular movements impairment

0 None

1 Signs only: subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort

2 Mild: subtle and barely clinically detectable weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware

3 Moderate: obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye

4 Marked: complete loss of movement in more than one direction of gaze in either eye

Nystagmus

0 None

1 Signs only or mild: gaze evoked nystagmus below the limits of "moderate"

2 Moderate: Sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance

3 Severe: sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

Trigeminal damage

0 None

1 Signs only

2 Mild: clinically detectable numbness of which patient is aware

3 Moderate: impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in last 24 hours)

4 Marked: unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

Facial Weakness

0 None

1 Signs only

2 Mild: clinically detectable facial weakness of which patient is aware

3 Moderate: incomplete facial palsy, such as weakness of eye closure that requires facial patching overnight or weakness of mouth closure that results in drooling

4 Marked: complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

Hearing loss

0 None

1 Signs only

2 Mild

3 Moderate: cannot hear finger rub and/or misses several whispered numbers

4 Marked: misses all or nearly all whispered numbers

Dysarthria

0 None

1 Signs only

2 Mild: Clinically detectable dysarthria of which patient is aware

3 Moderate: obvious dysarthria during ordinary conversation that impairs comprehensibility

4 Marked: incomprehensible speech

5 Inability to speak

Dysphagia

0 None

1 Signs only

2 Mild: difficulty with thin liquids

3 Moderate: difficulty with liquids and solid food

4 Marked: sustained difficulty with swallowing; requires a pureed diet

5 Inability to swallow

Other Bulbar functions

0 Normal

1 Signs only

2 Mild disability: clinically detectable deficit of which patient is usually aware

3 Moderate disability

4 Marked disability

Brainstem Functional system Score

0 Normal

1 Signs only

2a Moderate nystagmus

2b Other mild disability

3a Severe nystagmus

3b Marked extra-ocular weakness

3c Moderate disability of other cranial nerves

4a Marked dysarthria

4b Other marked disability

5 Inability to swallow or speak

(iii) Pyramidal Functions

Tendon Reflexes

0 Absent

1 Diminished

2 Normal

3 Exaggerated

4 Nonsustained clonus

5 Sustained clonus

Plantar Response

0 Flexor

1 Neutral or equivocal

2 Extensor

Limb Strength – BMRC Rating Scale

0 No muscle contraction detected

1 Visible contraction without visible joint movement

2 Visible movement only on the plane of gravity

3 Active movement against gravity

4 Active movement against resistance, but not full strength

5 Normal strength

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

0 None

1 Mild: barely increased muscle tone

2 Moderate: moderately increased muscle tone that can be overcome and full range of motion is possible

3 Severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible

4 Contracted

Gait spasticity

0 None

1 Barely perceptible

2 Evident: minor interference with function

3 Permanent shuffling: major interference with function

Pyramidal Function system Score

0 Normal

1 Abnormal signs without disability

2 Minimal Disability: Patient complains of fatiguability or reduced performance in strenuous motor tasks and/or BMRC grade 4 in one or two muscle groups

3a Mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two muscle groups; movements against gravity are possible

3b Severe monoparesis: BMRC grade 2 or less in one muscle group

4a Marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs

4b Moderate tetraparesis: BMRC grade 3 in three or more limbs

4c Monoplegia: BMRC grade 0 or 1 on one limb

5a Paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs

5b Hemiplegia

5c Marked tetraparesis: BMRC grade 2 or less in three or more limbs

6 Tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

(iv) Cerebellar Functional System Score

Truncal Ataxia

0 None

1 Signs only

2 Mild: Swaying with eyes closed

3 Moderate: Swaying with eyes open

4 Severe: unable to sit without assistance

Limb Ataxia (tremor/dysmetria and rapid alternating movements)

0 None

1 Signs only

2 Mild: tremor or clumsy movements easily seen, minor interference with function

3 Moderate: tremor or clumsy movements interfere with function in all spheres

4 Severe: most functions are very difficult

Tandem (straight line) walking

0 Normal

1 Impaired

2 Not possible

Gait ataxia

0 None

1 Signs only

2 Mild: abnormal balance only with tandem walking

3 Moderate: abnormal balance with ordinary walking

4 Severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another parson because of ataxia

Romberg test

0 Normal

1 Mild: mild instability with eyes closed

2 Moderate: not stable with eyes closed

3 Severe: not stable with eyes open

Note: The presence of severe gait ataxia alone (without severe truncal ataxia and sever ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness interferes with the testing of ataxia, score the patient's actual performeance, but also indicate the possible role of weakness by marking an 'X' after the cerebellar FS score.

Cerebellar Functional Systems Score

0 Normal
1 Abnormal signs without disability
2 Mild ataxia
3a Moderate truncal ataxia
3b Moderate limb ataxia
3c Moderate or severe gait ataxia
4 Severe truncal ataxia and severe ataxia in 3 or 4 limbs
5 Unable to perform coordinated movements due to ataxia
X Pyramidal weakness (BMRC grade 3 or worse in limb strength) interferes with cerebellar testing

(v) Sensory Functions

Superficial Sensation (Light touch and pain)

0 Normal
1 Signs only: slightly diminished sensation (temperature, figure writing) on formal testing of which patient is not aware
2 Mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 Moderate: impaired discrimination of sharp/dull
4 Marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 Complete loss: anaesthesia

Vibration Sensation (at the most distal joint)

0 Normal
1 Mild: graded tuning fork 5-7 of 8; alternatively, detects more than 10 seconds but less than examiner

2 Moderate: graded tuning fork 1-4 of 8; alternatively, detects between 2 and 10 seconds

3 Marked: complete loss of vibration sensation

Position sense

0 Normal

1 Mild: 1-2 incorrect responses, only distal joints affected

2 Moderate: misses many movements of fingers or toes; proximal joints affected

3 Marked: no perception of movement, astasia

Sensory Function System Score

0 Normal

1 Mild vibration or figure writing or temperature decrease only in one or two limbs

2a Mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs

2b Mild vibration or figure writing or temperature decrease alone in three or four limbs

3a Mild decrease in touch or pain or position sense and/or essentially lost vibration in one or two limbs

3b Mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs

4a Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs

4b Moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs

5a Loss (essentially) of sensation in one or two limbs

5b Moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head

6 Sensation essentially lost below the head

(vi) Bowel and Bladder Functions

Urinary hesitancy and retention

0 None

1 Mild: no major impact on lifestype

2 Moderate: urinary retention; frequent urinary tract infections

3 Severe: requires catheterisation

4 Loss of function: overflow incontinence

Urinary urgency and incontinence

0 None

1 Mild: no major impact on lifestype

2 Moderate: rare incontinence occurring no more than once a week; must wear pads

3 Severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads

4 Loss of function: loss of bladder control

Bladder catheterisation

0 None

1 Intermittent self catheterisation

2 Constant catheterisation

Bowel dysfunction

0 None

1 Mild: no incontinence, no major impact on lifestyle, mild constipation

2 Moderate: must wear pads or alter lifestyle to be near lavatory

3 Severe: in need of enemata or manual measures to evacuate bowel

4 Complete loss of function

Sexual dysfunction

0 None

1 Mild

2 Moderate

3 Severe

4 Loss of function

Note: When determining the EDSS step the bladder and bowel FS score is converted to a lower score as follows:

FS score – Converted FS score

1-1, 2-2, 3-3, 4-3, 5-4, 6-5.

Bowel and Bladder functional system score

0 Normal

1 Mild urinary hesitancy and/or urgency and/or rare urinary incontinence and/or severe constipation

2 Moderate urinary hesitancy and/or urgency and/or rare urinary incontinece and/or severe constipation

3 Frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowel

4 In need of almost constant catheterisation

5 Loss of bladder or bowel function; external or indwelling catheter

6 Loss of bowel and bladder function

(vii) Cerebral Functions

Depression and Euphoria

0 None

1 Present: patient complains of depression or is considered depressed or euphoric by the investigator or significant other

Decrease in Mentation

0 None

1 Signs only: not apparent to patient and/or significant other

2 Mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.

3 Moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time

4 Marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle

5 Dementia, confusion and/or complete disorientation

Note: the presence of depression and/or euphoria alone results in a Cerebral FS score of 1a, but does not affect the EDSS step. However a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step

Functional System Score

0 Normal

1a Mood alteration (depression and/or euphoria) alone (does not affect EDSS step)

1b Mild fatigue; signs only decrease in mentation

2 Mild decrease in mentation; moderate or severe fatigue

3 Moderate decrease in mentation

4 Marked decrease in mentation

5 Dementia

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