PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Multiple sclerosis? the disease and its manifestations

W. I. McDonald and M. A. Ron

Phil. Trans. R. Soc. Lond. B 1999 **354**, 1615-1622
doi: 10.1098/rstb.1999.0506

THE ROYAL SOCIETY

Multiple sclerosis: the disease and its manifestations

W. I. McDonald[1*] **and M. A. Ron**[2]

[1]*Royal College of Physicians, 11 St Andrews Place, London NW1 4LE, UK*
[2]*Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK*

Multiple sclerosis is an immune-mediated inflammatory demyelinating disease of the central nervous system clinically characterized by relapses and remissions of neurological disturbance. A typical relapse, exemplified by optic neuritis, increases in severity over a week or two and after approximately one month begins to remit. Resolution takes place over the course of two to three months. In the early stages, clinical recovery is virtually complete, though persistent abnormalities of conduction can usually be detected by evoked potential techniques and persistent structural abnormalities can be detected by magnetic resonance imaging (MRI). These techniques, together with cerebrospinal fluid examination for oligoclonal IgG, provide supporting evidence for the diagnosis which, in the absence of a specific test, nevertheless remains primarily clinical. The course of the disease is very variable, but after a number of years neurological deficit begins to accumulate after each relapse. In most patients, the relapsing and remitting phase of the disease is followed by a phase of continuous progression of disability. Cognitive disturbances can be detected in many patients even quite early in the course of the illness. Deficits in attention, memory and executive skills may be prominent and tend to become increasingly prominent as neurological deficit increases, although this is not always the case. There is some correlation between the extent of MRI abnormalities in the cerebral white matter and the severity of cognitive deficit. Depression and anxiety are commonly experienced but are poorly correlated to the lesion load seen on MRI. In contrast, the much rarer psychotic symptoms, euphoria and emotional lability are closely linked to the severity of white matter disease.

Keywords: multiple sclerosis; magnetic resonance imaging; relapse; remission; cognition; psychiatric impairment

1. INTRODUCTION

Multiple sclerosis (MS) is one of the commonest disabling neurological diseases of young adults in populations of northern European origin; it is a major source of economic loss. The cardinal pathological features are (i) focal areas (plaques) of demyelination, usually perivenular in orientation with relative preservation of axonal continuity, (ii) immune-mediated inflammation, and (iii) astrocytic gliosis. In the great majority of patients the illness is characterized by relapses and remissions of neurological disturbance which are attributable to the acute development of plaques at clinically eloquent sites. Although lesions can occur anywhere in the central nervous system, there are certain sites of predilection, the involvement of which (e.g. the optic nerve, brainstem, cerebellum and spinal cord) leads to obvious clinical deficits, while the involvement of others (e.g. the cerebral periventricular white matter) does not. The mean age of onset is 31 years and the illness is approximately three times as common in women as in men. The course of the illness is enormously variable. At one extreme, rare cases are fatal in less than a year. At the other, occasional patients have little disability even after 50 years. However, the majority, after an initially relapsing and remitting course, enter a phase in which there is continuous deterioration (known as secondary progression) superimposed on which may be acute exacerbations of neurological deficit.

The frequency of relapses varies widely, though on average it is approximately 0.8–1.0 per annum (Ebers 1998). Exceptionally, one, two or even three decades may intervene. In a minority of patients the illness is steadily progressive from its onset without a clear-cut relapse or remission at any stage. This is the primary progressive form of the disease. At post-mortem the findings using standard methods are indistinguishable from those in the other forms of the disease. There has been debate as to whether this form of the illness is in fact a distinct entity (McDonald & Thompson 1997; Thompson *et al.* 1997). However, there are no consistent specifically different features, though the course (which however resembles that of secondary progressive MS without preceding relapses) and evidence for a rather low level of inflammatory activity in the lesions are characteristic (Thompson *et al.* 1991; Revesz *et al.* 1994). The present consensus is that the relapsing–remitting, secondary progressive and primary progressive forms of MS represent a spectrum of manifestations of a single disease process.

* Author for correspondence (williamian@yahoo.com).

The time-course of an individual relapse is characteristic: the symptoms usually increase from onset to reach a maximum after one or two weeks. After a few further weeks recovery begins and continues for two to three months. Early in the course of the illness, recovery from individual episodes is often virtually complete. Later, however, residual deficit accumulates, leading to progressive interference with family life and work.

The total duration of the illness also varies widely. The median survival from onset is 28 years for men and 33 years for women (Bronnum-Hansen *et al.* 1994). This broad statement hides the burden of disability which is so common: 40% of patients require assistance in walking after 15 years (Weinshenker *et al.* 1989) and loss of bladder and bowel control ultimately occurs in almost all patients. These features predispose to infection which is a common cause of death; death directly from MS itself is rare.

2. THE SYMPTOMATOLOGY OF MULTIPLE SCLEROSIS

The common ways for MS to present are weakness, tingling or numbness in the limbs, vertigo and double vision or visual loss, reflecting the sites of predilection for plaques. Each of these features can of course first appear later in the course of the illness. Other features which commonly do so are bladder and bowel disturbance (often progressing to incontinence) and cognitive dysfunction. A particularly troublesome symptom which is poorly understood is a sense of fatigue unrelated to weakness. It is common and in some patients disabling. Two manifestations of MS (optic neuritis and cognitive disturbance) are discussed in more detail below because of their frequency and because they are good examples of the problems which the disease presents.

3. DIAGNOSIS OF MULTIPLE SCLEROSIS

There is no specific test for MS and the diagnosis is still primarily clinical. It depends on the demonstration of at least two necessarily separate sites of central nervous system damage in an individual with a history of at least two episodes of neurological disturbance of the kind encountered in MS. There is no difficulty in the established case, but considerable problems arise early in the course of the disease. Here advances in the techniques of investigation of central nervous system structure, function and immunological status have helped greatly, when, for example, recovery from a previous episode has been so good that no residual abnormal physical signs are detectable on examination. Modern diagnostic criteria incorporate the results of these investigations (Poser *et al.* 1983). The techniques fall into two broad categories: those which detect clinically occult ('silent') lesions and those which detect an abnormality of immunological function in relation to the central nervous system.

(a) *Detection of occult lesions: evoked potentials*

Exploitation of the observation that demyelination produces a slowing of conduction in demyelinated nerve fibres (McDonald 1963; McDonald & Sears 1970) led to the introduction of evoked potential techniques as a means of assessing function in sensory (and later motor) (Cowan *et al.* 1984) pathways. The first and, in the event, most useful of these techniques to be introduced was the pattern reversal visual-evoked potential (VEP) (Halliday *et al.* 1972). Substantial delays in the p100 (on average *ca.* 35 ms; Halliday *et al.* 1973) are found in acute optic neuritis. These delays usually persist despite complete recovery of visual acuity. Thus, VEPs can be used to detect the presence of an occult lesion and often do so even when there is no history of previous visual disturbance. By virtue of the delay, a VEP can also indicate the probability that the lesion is demyelinating in nature. The VEP is abnormal in 90% of patients with clinically definite MS (reflecting the frequency of involvement of the optic nerve) and in *ca.* 75% overall, when patients with less definite diagnoses are included. Somatosensory, brainstem auditory and motor-evoked potentials have comparable though in practice less useful roles in diagnosis. It must be emphasized that delays in evoked potentials are not confined to MS, but occur with demyelination arising from any cause including compression by tumour. The results must be interpreted in the light of the rest of the clinical and investigative picture.

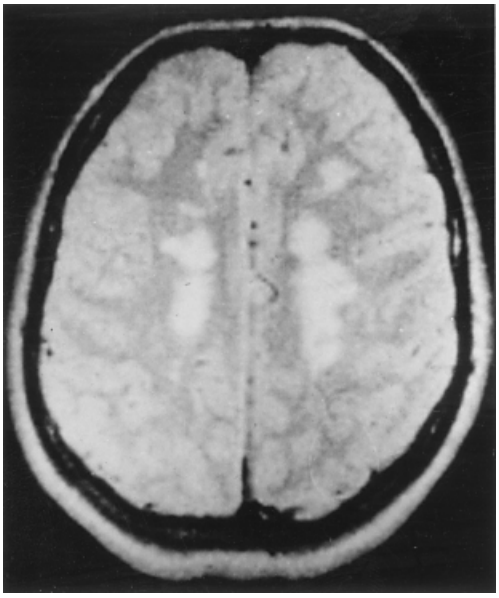

Figure 1. Proton-density weighted MRI of the cerebral hemispheres in multiple sclerosis. The white (high-signal) areas in both hemispheres represent the lesions of MS.

(b) *Magnetic resonance imaging*

The single most informative innovation in the investigation of multiple sclerosis in recent years has been the application of nuclear magnetic resonance (NMR) methods. From the diagnostic point of view, magnetic resonance imaging (MRI) is invaluable. Areas of abnormality in T2-weighted or proton-density weighted images (figure 1) in a distribution corresponding to that found at post-mortem occur in more than 95% of patients with clinically definite disease (Ormerod *et al.* 1987) and even in approximately two-thirds of patients presenting with an isolated clinical syndrome of the kind seen in MS (e.g. optic neuritis or acute myelopathy). The changes are not specific but the pattern is highly charac-

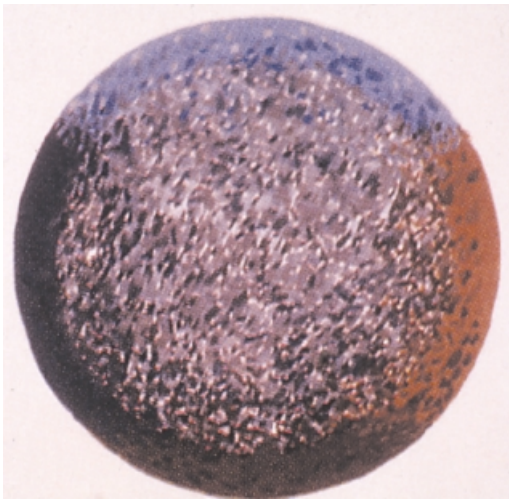

Figure 2. Painting by Peter MacKarell of what he saw through the affected eye early in the development of an acute attack of optic neuritis.

Figure 3. Another painting by Peter MacKarell of what he saw through the affected eye during the early stages of recovery from optic neuritis. His description of the scene is quoted in the text.

teristic and, when taken together with other data, often provide crucial confirmatory evidence for the diagnosis. MRI is also the best method available for excluding potentially curable lesions such as benign tumours compressing the spinal cord or the optic nerve, which may simulate the progressive manifestations of MS. The role of NMR techniques in understanding the pathogenesis and pathophysiology of MS is discussed in other papers in this issue.

(c) *Immunological abnormalities: cerebrospinal fluid*

Diagnostic lumbar puncture has been performed in suspected multiple sclerosis for more than 75 years because it provides information about the existence of inflammation through a raised cell count and protein level (Greenfield & Carmichael 1925). The most important development has been the introduction of isoelectric focusing in cerebrospinal fluid (CSF) protein electrophoresis. Oligoclonal IgG is found in 95% of patients with clinically definite disease (Andersson *et al*. 1994) and (like abnormal VEPs and MRI) is predictive of its future development in patients presenting with isolated clinical syndromes (e.g. optic neuritis, brainstem syndromes and myelopathy) (Moulin *et al*. 1983). As with the other investigations mentioned, the changes are not specific but in the appropriate clinical context can be diagnostically decisive. Since the introduction of MRI, lumbar puncture is less often needed but, in complex cases, the demonstration of an immunological abnormality in relation to the central nervous system may be particularly helpful.

4. OPTIC NEURITIS

Acute optic neuritis is one of the commonest causes of spontaneously reversible severe visual loss in young adults of northern European origin. It is the presenting feature of MS in approximately one-fifth of patients and occurs at some stage in its course in approximately three-quarters of patients (Shibasaki *et al*. 1981). That having been said, in between one-half and three-quarters of cases of optic neuritis, no other cause is found even after prolonged follow-up; it is to be noted, however, that cases are on record of MS appearing after more than three decades (see the review by McDonald 1999).

A number of risk factors for the development of the clinically disseminated disease after optic neuritis have been identified: the presence of retinal perivascular sheathing (see below), oligoclonal bands in the CSF and, of most significance, the presence of clinically 'silent' cerebral lesions by MRI. Between one-half and two-thirds of patients exhibit such abnormalities at presentation (McDonald 1999) and, after ten years, 91% of those with such abnormalities have developed clinically definite MS, compared with 6% of those without (O'Riordan *et al*. 1998).

The clinical picture of optic neuritis is highly characteristic. Blurring of vision, often preceded by mild discomfort behind the eye, is the commonest mode of onset. Visual impairment progresses to reach a maximum usually within one to two weeks. At this stage there may be no perception of light, though more often the individual is aware of marked central impairment with relative preservation of peripheral vision (figure 2). Colour vision is impaired and in mild cases may be the only abnormality noticed by the patient or detected on clinical examination. Spontaneous flashes of light (phosphenes) often precipitated by eye movement, occur in approximately one-third of patients (Lightman *et al*. 1987).

The peculiar dynamic quality of the distorted visual perceptions was beautifully expressed by MacKarell (1986, 1990), a professional painter who experienced several attacks of optic neuritis and later died of MS. He recorded his experience in words and in paintings, some of the originals of the latter being now in Guy's Hospital and others in the Moorfields Eye Hospital. The following is taken from one of his accounts.

> One evening my lad asked me to look up a word in the French dictionary and I found that I could not make out the print because at each point I attempted to focus, the

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

> individual letters were obscured by an infuriating and irritating bouncing grey dot . . . . The next day, upon waking I discovered that there was, over the central zone of vision of my right eye, what seemed like a grey asbestos mat. (see figure 2) . . . . In three days all response was lost. (MacKarell 1986, p. 285)

After approximately two weeks, he began to improve.

> I became aware that through the murk I could make out the fingers of my right hand as I waggled them in front of my right eye. The feeling was like peering through a thick screen of dirty net curtains or butter muslin. . . . When the ophthalmoscope was shone into my right eye I was delighted to note that the head of light appeared as a lovely cobalt blue. It seemed to shine like an astronomic phenomenon in interstellar space. [Later] I began to notice that my appreciation of space was wayward. (see figure 3) . . . To my amazement I became aware that as I lay in bed that the metal curtain rail which surrounded the bed-space seemed to wobble in and out of the background of the opposite wall. There was an arch opposite and far from receding, the way a 'dark' or 'void' normally does, this shape too lurched and obtruded, seemingly advancing out of the background. There was a window in this arch and it seemed that the same mutinous quality made it refuse to 'sit' in space. Surfaces appeared liquid rather than solid. . . . (MacKarell 1986, p. 287)

He made a virtually full recovery, but later had a second episode. He was at the Royal Ballet with his daughter for a performance of Cinderella. Through the newly affected eye the Ugly Sisters dressed for the ball

> . . . were quite transformed—to me they shimmered and glittered in an unreal spectacle that was, if anything, staggeringly beautiful . . . I began to really enjoy the iridescence for it was like having a neoimpressionist painting—a Seurat or Signac—magically dancing about in the visual field of the affected eye. (MacKarell 1986, p. 291)

However, some of the impressions were disturbing. A painting of his daughter in a park

> . . . records a strange, disturbing, recurrent (and perhaps the most enduring) feature which I call the 'incipient dissolve'. It is as if the coherence and integration of vision including the admission of light was about to fragment and fade like a cinematic device. (MacKarell 1986, p. 292)

Examination of the patient reveals a uniocular field defect, characteristically a central scotoma, though variations are encountered both in the earliest stages and during recovery. Ophthalmoscopically the optic nerve head is swollen in approximately one-third of patients and in approximately one-half there is later optic atrophy and 'slits' in the nerve fibre layer signalling the degeneration of bundles of axons (Frisén & Hoyt 1974). In approximately one-quarter of patients perivenular sheathing is visible at the periphery of the retina (Lightman *et al.* 1987). Fluoroscein angiography reveals a breakdown of the blood–retinal barrier at such sites; histologically there is perivenular infiltration with inflammatory cells (Fog 1965; Arnold *et al.* 1984). There is a close parallel between these features and the breakdown of the blood–brain barrier demonstrated by gadolinium-DTPA enhancement in MRI seen in association with perivenular inflammation in the new cerebral lesion in multiple sclerosis (Katz *et al.* 1993). The absence of myelin from the retina suggests that local myelin antigens are not necessary for the development of the characteristic vascular inflammatory events which herald the onset of the new lesion (see Lassman, this issue; Smith & McDonald, this issue). The initiating event in optic neuritis, as in the relapses of MS, is at present obscure. It may lie outside the central nervous system since the only known precipitating factor for relapse is intercurrent viral infection (Sibley *et al.* 1985) and, when a relapse occurs, it is common to find multiple areas of blood–brain barrier breakdown by gadolinium-enhanced MRI involving other, widely separated areas in addition to that related to the new symptoms (Grossman *et al.* 1986).

(a) *Recovery*

As MacKarrell's (1986) account revealed, excellent recovery of visual acuity is usual, at least in the early episodes. It usually starts one or two weeks after the visual disturbance has reached its worst and proceeds over the following one or two months; sometimes the best acuity is not achieved for more than six months. Despite the strikingly good recovery of visual acuity, careful testing often reveals subtle field defects (corresponding to the regions of retinal nerve fibre loss), impairment of colour vision and contrast sensitivity (Hess & Plant 1986). There is also a range of dynamic symptoms to which little attention has so far been devoted. For example, patients may have difficulty in judging the relationship between the body (or one of its parts) and rapidly moving objects. This leads, for example, to difficulty in playing table tennis (as in one of our patients who was a highly skilled university player) and in crossing the road in moving traffic. Whether this relates to the existence of the Pulfrich effect (readily demonstrated in the clinic), when a unilateral attack of optic neuritis leads to a substantial difference in the latency of the cortical response to stimulation of the two eyes (Rushton 1975; Smith & McDonald 1999) or to involvement of fibres mediating motion perception in the visual pathway or the cerebral cortex is yet to be decided.

5. COGNITIVE AND PSYCHIATRIC IMPAIRMENT

Cognitive impairment is subtle in patients with clinically isolated syndromes and subjective symptoms are, as a rule, absent. The slowing of cognitive processing and impaired auditory attention were first reported in a group of patients with different clinical presentations (i.e. optic neuritis and brainstem or cord syndromes) who exhibited 'silent' MRI abnormalities in other brain regions (Callanan *et al.* 1989). These findings were later confirmed in a group of patients with optic neuritis who had white matter lesions elsewhere in the brain compared to those who did not (Feinstein *et al.* 1992*b*). In addition, impairment of working memory has been described in patients presenting with clinically isolated myelopathy (Pelosi *et al.* 1997). In that study, event-related potentials data suggested that both acquisition of memory traces and retrieval processes are impaired.

In patients with clinically definite multiple sclerosis, cognitive abnormalities can be detected in 40–60% of

patients and contribute significantly to the burden of disability (Rao *et al.* 1991*b*). A pattern of cognitive abnormalities characterized by a decline in intellectual ability, as measured by the difference between current and estimated pre-morbid IQ, has been documented in 60% of clinically definite MS patients attending hospital. In addition, memory and executive functions are often impaired to an extent that cannot be explained as a result of the general intellectual decline (Ron *et al.* 1991).

(a) *Memory tasks*

Impairment in memory tasks is characterized by poor recall, with better preserved recognition and normal forgetting (Rao *et al.* 1991*a*). This dissociation has also been reported in Huntington's disease and other conditions predominantly affecting subcortical structures. In some studies verbal memory appeared to be less impaired than visual memory (Ron *et al.* 1991). A dissociation between memory and attention deficits has been reported (Litvan *et al.* 1988), suggesting that the former is not sufficient explanation for memory impairment which is more likely to result from defective retrieval (Ryan *et al.* 1996).

(b) *Executive functions deficits*

Executive functions deficits appear to be equally common. Impairment in working memory (Litvan *et al.* 1988; Grafman *et al.* 1990; Foong *et al.* 1997), verbal fluency, use of strategy, planning and cognitive estimates have also been described (Foong *et al.* 1997), although not all executive functions are impaired to the same extent. Foong *et al.* (1997) described relative preservation of planning ability with a pattern of deficits reminiscent of that found in HIV dementia, another white matter disease.

(c) *Language abilities*

Language abilities have traditionally been considered to be spared by the disease, but Kujala *et al.* (1996) described subtle abnormalities even in patients with mild cognitive impairment. These abnormalities, which involve semantic and circumlocutory naming errors, could not be explained as resulting from other cognitive abnormalities which were often absent in this sample.

(d) *Natural history*

The natural history of these cognitive deficits is only partially understood. It is well established that cognitive deficits may remain static for many patients during the early stages of the disease (Kujala *et al.* 1996, 1997; Hohol *et al.* 1997). A four-year follow-up study of patients with clinically isolated lesions (Feinstein *et al.* 1992*b*) found that cognitive deterioration had only occurred in those who had developed clinically definite MS and particularly in those with secondary progressive disease. In such patients, declines in auditory attention and visual memory were observed. Other follow-up studies (Amato *et al.* 1995) suggested that other deficits (i.e. linguistic disturbances and impaired abstract reasoning) emerge as the disease progresses, although the pattern of impairment varies from patient to patient.

The effects of relapses and remissions on cognitive ability are poorly understood. In a serial study testing patients every two weeks, performance on tests of attention and information processing speed declined only in those in whom there was an increase in MRI lesion load (Feinstein *et al.* 1993). In a group of patients tested during a relapse and again six weeks later, Foong *et al.* (1998) described improvements in attention tasks only in those who were mildly impaired at the outset and in whom the volume of gadolinium-enhancing lesions diminished between tests. Memory impairment remained unchanged in all patients, suggesting that, for some patients, cognitive deficits, particularly memory impairment, may be permanent.

Cognitive impairment tends to be more severe in those with secondary progressive disease (Ron *et al.* 1991; Amato *et al.* 1995; Patti *et al.* 1995), but cases of early severe cognitive impairment with only mild neurological disability are well documented (Fontaine *et al.* 1994). Cognitive decline cannot be fully explained as a result of fatigue or depression (Grossman *et al.* 1994). Patients with primary progressive MS have been thought to have more severe cognitive deficits than those with secondary progressive disease (Comi *et al.* 1995), but this has been questioned in a more recent study (Foong *et al.* 1999).

Cognitive impairment has been found to correlate with MRI markers of disease, the most widely used of them being T2 lesion load (Ron *et al.* 1991), although even at best clinico-MRI correlations are only modest. The lack of neuropathological specificity of T2 abnormalities and the presence of pathology in the normal-appearing white matter account for the limited correlations. Other MRI parameters such as T1 lesion load and degree of brain atrophy may be better correlated with cognitive impairment, but reports are contradictory (Rovaris *et al.* 1998) and other techniques such as magnetization transfer and diffusion tensor imaging, sensitive indices of axonal and myelin integrity, may be more valuable in establishing the neuropathological substrate of cognitive deficits (Rovaris *et al.* 1998).

Attempts to link regional MRI abnormalities (i.e. frontal lesion load) with specific cognitive deficits (i.e. executive functions) have met with variable success (Arnett *et al.* 1994; Foong *et al.* 1997) as could be expected in the presence of widespread, multiple lesions and generalized normal-appearing white matter abnormalities. Functional imaging studies hold greater promise of determining the common neural networks disrupted by lesions in different localizations. The positron emission tomography study of Paulesu *et al.* (1996) went some way towards achieving this aim. Decreased glucose metabolism in the hippocampi and left thalamus was present in MS patients with memory impairment compared to those without. These changes in brain metabolism, which occurred in the absence of detectable temporal or thalamic lesions, may be caused by more distant or subtle pathology and are likely to represent the common substrate for these deficits.

6. PSYCHIATRIC ABNORMALITIES IN MULTIPLE SCLEROSIS

Psychiatric morbidity is not increased in patients with clinically isolated syndromes (Logsdail *et al.* 1988) and there is little evidence that symptoms of depression or anxiety, without concomitant neurological symptoms or

signs, are the presenting features of MS (Skegg *et al.* 1988). On the other hand, psychiatric morbidity is high in patients with clinically definite MS.

(a) *Depression*

The prevalence of depression is close to 50% in hospital attenders (Ron & Logsdail 1989); this is higher than in patients attending with non-neurological disability (due, for example, to rheumatoid arthritis) and the lifetime risk of developing depression is of the same order (Sadovnik *et al.* 1996). A sevenfold increase in suicide has also been reported (Sadovnik *et al.* 1991).

Low mood, feelings of anxiety, irritability and anger and somatic preoccupations are the commonest psychiatric features. The presence of depression is not closely related to the duration of illness or degree of disability or cognitive impairment, but may be commoner during relapses or when neurological disability is progressive. There is little to support a genetic predisposition, as illustrated by the fact that there is no increased lifetime risk of depression in first-degree relatives of depressed MS patients (Sadovnick *et al.* 1996). Environmental factors, on the other hand, are clearly important in determining psychiatric morbidity and the degree of social stress and lack of support, as perceived by the patients, correlates more closely with the presence of depression than other features of the illness or the severity of MRI abnormalities (Ron & Logsdail 1989).

The increased rates of psychiatric morbidity in patients with MS and other brain diseases argue in favour of a causative role, although correlations with MRI lesion load have been disappointing (Ron & Logsdail 1989; Pujol *et al.* 1997). Recent studies have focused on fronto-temporal circuits known to be relevant in depression and, as with cognitive impairment, a pattern starts to emerge. Thus, Pujol *et al.* (1997) described an association between depressive symptoms and lesions in the arcuate fasciculus, while Sabatini *et al.* (1996) reported perfusion asymmetries in the limbic system (relatively higher cerebral blood flow on the left) in MS patients in association with depression. A correlation between the presence of depression and inflammation markers (gadolinium-enhancing lesions and white cells in the CSF) has also been reported (Fassbender *et al.* 1998).

(b) *Bipolar affective disorder*

Bipolar affective disorder has been reported to occur more often in MS patients than in the general population (Schiffer *et al.* 1986), but this remains to be confirmed by appropriate epidemiological studies. A number of intriguing studies have suggested that unsuspected MS may be commoner than what might be expected by chance in psychiatric in-patients. Thus, Pine *et al.* (1995) reported this to be the case in those admitted with mania and Lyoo *et al.* (1996) found that less than 1% of psychiatric patients referred for MRI scans had abnormalities of the white matter compatible with MS patients, with frontal lobe lesions present in 75%. The most common diagnosis was one of affective illness which tended to be more severe and protracted than in those with normal MRI. It is unclear how these findings relate to the presence of white matter hyperintensities, which are often reported in patients with 'primary' affective disorders.

(c) *Psychotic episodes*

Short-lived psychotic episodes with schizophrenic or affective symptomatology have also been described (Feinstein *et al.* 1992*a*), but they appear to be uncommon. These episodes occurred when neurological disability was well established and temporal lobe lesions appeared to be particularly prominent in these patients. This is in marked contrast with the high incidence of schizophrenia-like psychosis in patients with metachromatic leucodystrophy (Hyde *et al.* 1992), suggesting that the age of onset of white matter disease (i.e. during childhood in the case of metachromatic leucodystrophy) may lead to very different psychiatric manifestations.

(d) *Euphoria*

Euphoria is an uncommon symptom, with a prevalence of *ca.* 10% and is closely associated with the presence of brain pathology and cognitive impairment (Ron & Logsdail 1989). Euphoria is best defined as a state of persistent cheerfulness without the motor overactivity of mania and is best considered as the type of personality change akin to that seen in patients with frontal lobe pathology. Pathological laughing and crying, an abnormal display of emotion not associated with the presence of depression, is equally uncommon. In a recent study (Feinstein *et al.* 1997), the symptom was not associated with disease exacerbations, but it was commoner in severely disabled patients with cognitive impairment. Earlier studies have described an association with pontine, brainstem and periventricular lesions (Reisches *et al.* 1988).

REFERENCES

Amato, M. P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G. & Amaducci, L. 1995 Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch. Neurol.* **52**, 168–172.

Andersson, M. (and 23 others) 1994 Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J. Neurol. Neurosurg. Psychiatr.* **57**, 897–902.

Arnett, P. A., Rao, S. M., Bernardin, L., Grafman, J., Yetkin, F. Z. & Lobeck, L. 1994 Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. *Neurology* **44**, 420–425.

Arnold, A. C., Pepose, J. S., Heplerth, S. & Foos, R. Y. 1984 Retinal periphlebitis and retinitis in multiple sclerosis. I. Pathologic characteristics. *Ophthalmology* **91**, 255–261.

Bronnum-Hansen, H., Koch-Henriksen, N. & Hyllested, K. 1994 Survival of patients with multiple sclerosis in Denmark: a nationwide, long term epidemiologic survey. *Neurology* **44**, 1901–1907.

Callanan, M. M., Logsdail, S. J., Ron, M. A. & Warrington, E. K. 1989 Cognitive impairment in patients with clinically isolated lesions of the type seen in multiple sclerosis: a psychometric and MRI study. *Brain* **112**, 361–374.

Comi, G., Filippi, M., Martinelli, V., Campi, A., Rodegher, M., Alberoni, M., Sirabian, G. & Canal, N. 1995 Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. *J. Neurol. Sci.* **132**, 222–227.

Cowan, J. M. A., Dick, J. P. R., Day, B. L., Rothwell, J. C., Thompson, P. D. & Marsden, C. D. 1984 Abnormalities in central motor pathway conduction in multiple sclerosis. *Lancet* **ii**, 304–307.

Ebers, G. 1998 Natural history of multiple sclerosis. In *McAlpine's multiple sclerosis*, 3rd edn (ed. A. Compston, G. Ebers, H. Lassmann, I. McDonald, B. Matthews & H. Wekerle), pp. 191–221. London: Churchill Livingstone.

Fassbender, K., Schmidt, R., Mössner, R., Kischka, U., Kühnen, J., Schwartz, A. & Hennerici, M. 1998 Mood disorders and dysfunction of the hypothalamic–pituitary–adrenal axis in multiple sclerosis. *Arch. Neurol.* **55**, 66–72.

Feinstein, A., Du Boulay, G. & Ron, M. A. 1992*a* Psychotic illness in multiple sclerosis: a clinical and magnetic resonance imaging study. *Br. J. Psychiatr.* **161**, 680–685.

Feinstein, A., Kartsounis, L., Miller, D., Youl, B. & Ron, M. A. 1992*b* Clinically isolated lesions of the type seen in multiple sclerosis followed up: a cognitive, psychiatric and MRI study. *J. Neurol. Neurosurg. Psychiatr.* **55**, 869–876.

Feinstein, A., Ron, M. & Thompson, A. 1993 A serial study of psychometric and magnetic resonance imaging changes in multiple sclerosis. *Brain* **116**, 569–602.

Feinstein, A., Feinstein, K., Gray, T. & O'Connor, P. 1997 Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. *Arch. Neurol.* **54**, 1116–1121.

Fog, T. 1965 The topography of plaques in multiple sclerosis with special reference to cerebral plaques. *Acta Neurol. Scand.* **41** (Suppl. 15), 1–161.

Fontaine, B. (and 9 others) 1994 Dementia in two histologically confirmed cases of multiple sclerosis: one case with isolated dementia and one case associated with psychiatric symptoms. *J. Neurol. Neurosurg. Psychiatr.* **57**, 353–359.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., Miller, D. H. & Ron, M. A. 1997 Executive function in multiple sclerosis: the role of frontal lobe pathology. *Brain* **120**, 15–26.

Foong, J., Rozewicz, L., Quaghebeur, G., Thompson, A. J., Miller, D. H. & Ron, M. A. 1998 Neuropsychological deficits in MS after acute relapse. *J. Neurol. Neurosurg. Psychiatr.* **64**, 529–532.

Foong, J., Rozewicz, L., Chong, W. K., Thompson, A. J., Miller, D. H. & Ron, M. A. 1999 A comparison of neuropsychological deficits in primary and secondary progressive MS. *J. Neurol.* (Submitted.)

Frisén, L. & Hoyt, W. F. 1974 Insidious atrophy and retinal nerve fibres in multiple sclerosis. Fundoscopic identification in patients with and without visual complaint. *Arch. Ophthalmol.* **92**, 91–97.

Grafman, J., Rao, S. M. & Litvan, I. 1990 Disorders of memory. In *Neurobehavioural aspects of multiple sclerosis* (ed. S. M. Rao), pp. 102–117. New York: Oxford University Press.

Greenfield, J. G. & Carmichael, E. A. 1925 *The cerebrospinal fluid in clinical diagnosis*. London: Macmillan.

Grossman, R. I., Gonzales-Scarano, F., Atlas, S. W., Galetta, S. & Silberberg, D. H. 1986 Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* **161**, 721–725.

Grossman, M. (and 13 others) 1994 Patterns of cognitive impairment in relapsing–remitting and chronic progressive multiple sclerosis. *Neuropsychiatr. Neuropsychol. Behav. Neurol.* **7**, 194–210.

Halliday, A. M., McDonald, W. I. & Mushin, J. 1972 Delayed visual evoked response in optic neuritis. *Lancet* **I**, 982–985.

Halliday, A. M., McDonald, W. I. & Mushin, J. 1973 Delayed pattern-evoked responses in optic neuritis in relation to visual acuity. *Trans. Ophthalmol. Soc. UK* **93**, 315–324.

Hess, R. F. & Plant, G. T. 1986 The psychophysical loss in optic neuritis; spatial and temporal aspects. In *Optic neuritis* (ed. R. F. Hess & G. T. Plant), pp. 109–151. Cambridge University Press.

Hohol, M. J., Guttmann, C. R. G., Orav, J., Glenn, A. M., Kikinis, R., Khoury, S. J., Jolesz, F. A. & Weiner, H. L. 1997 Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. *Arch. Neurol.* **54**, 1018–1025.

Hyde, T. M., Ziegler, J. C. & Weinberger, D. R. 1992 Psychiatric disturbances in metachromatic leukodystrophy: insights into the neurobiology of psychosis. *Arch. Neurol.* **49**, 401–406.

Katz, D., Taubenberger, J. K., Cannella, B., McFarlin, D. E., Raine, C. S. & McFarland, H. F. 1993 Correlation between magnetic resonance imaging findings and lesion development in chronic, active multiple sclerosis. *Ann. Neurol.* **34**, 661–669.

Kujala, P., Portin, R. & Ruutiainen, J. 1996 Language functions in incipient cognitive decline in multiple sclerosis. *J. Neurol. Sci.* **141**, 79–86.

Kujala, P., Portin, R. & Ruutiainen, J. 1997 The progress of cognitive decline in multiple sclerosis: a controlled 3 year follow-up. *Brain* **120**, 289–297.

Lightman, S., McDonald, W. I., Bird, A. C., Francis, D. A., Hoskins, A., Batchelor, J. R. & Halliday, A. M. 1987 Retinal venous sheathing in optic neuritis. Its significance for the pathogenesis of multiple sclerosis. *Brain* **110**, 405–414.

Litvan, I., Grafman, J., Vendrell, P., Martinez, J. M., Junque, C., Vendrell, J. M. & Barraquer-Bordas, J. L. 1988 Multiple memory deficits in patients with multiple sclerosis: exploring the working memory system. *Arch. Neurol.* **45**, 607–610.

Logsdail, S. J., Callanan, M. M. & Ron, M. A. 1988 Psychiatric morbidity in patients with clinically isolated lesions of the type seen in multiple sclerosis: a clinical and MRI study. *Psychol. Med.* **18**, 355–364.

Lyoo, I. K., Seol, H. Y., Byun, H. S. & Renshaw, P. F. 1996 Unsuspected multiple sclerosis in patients with psychiatric disorders: a magnetic resonance imaging study. *J. Neuropsychiatr. Clin. Neurosci.* **8**, 54–59.

McDonald, W. I. 1963 The effects of experimental demyelination on conduction in peripheral nerve: a histological and electrophysiological study. II. Electrophysiological observations. *Brain* **86**, 501–524.

McDonald, W. I. 1999 Physicians, subsequence and consequence. *J. Neurol. Neurosurg. Psychiatr.* (In the press.)

McDonald, W. I. & Sears, T. A. 1970 The effects of experimental demyelination on conduction in the central nervous system. *Brain* **93**, 583–598.

McDonald, W. I. & Thompson, A. J. 1997 How many kinds of multiple sclerosis are there? In *Multiple sclerosis: clinical challenges and controversies* (ed. A. J. Thompson, C. Polman & R. Hohlfeld), pp. 35–42. London: Martin Dunitz.

MacKarell, P. 1986 Interior journey and beyond: an artist's view of optic neuritis. In *Optic neuritis* (ed. R. F. Hess & G. T. Plant), pp. 283–293. Cambridge University Press.

MacKarell, P. 1990 Interior journey and beyond: an artist's view of optic neuritis (pp. 18–29); and The odyssey (pp. 30–59). In *Depictions of an odyssey* (ed. S. Paine). Corsham: Corsham National Society for Education in Art & Design.

Moulin, D., Paty, D. W. & Ebers, G. C. 1983 The predictive value of cerebrospinal electrophoresis in 'possible' multiple sclerosis. *Brain* **106**, 809–816.

O'Riordan, J. I., Thompson, A. J., Kingsley, D. P. E., McManus, D. C., Kendall, B. E., Rudge, P., McDonald, W. I. & Miller, B. H. 1998 The prognostic value of MRI in clinically isolated syndromes of the CNS. A 10-year follow up. *Brain* **121**, 495–503.

Ormerod, I. E. C. (and 14 others) 1987 The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. *Brain* **110**, 1579–1616.

Patti, F., Di Stefano, M., De Pascalis, D., Ciancio, M. R., De Bernardis, E., Nicoletti, F. & Reggio, A. 1995 May there exist specific MRI findings predictive of dementia in multiple sclerosis patients? *Funct. Neurol.* **10**, 83–90.

Paulesu, E. (and 13 others) 1996 Functional basis of memory impairment in multiple sclerosis: a [18F]FDG PET study. *Neuroimage* **4**, 87–96.

Pelosi, L., Geesken, J. M., Holly, M., Hayward, M. & Blumhardt, L. D. 1997 Working memory impairment in early multiple sclerosis. Evidence from an event-related potential study of patients with clinically isolated myelopathy. *Brain* **120**, 2039–2058.

Pine, D. S., Douglas, C. J., Charles, E., Davies, M. & Kahn, D. 1995 Patients with multiple sclerosis presenting to psychiatric hospitals. *J. Clin. Psychiatr.* **56**, 297–306.

Poser, C. M., Paty, P. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Silberberg, D. H. & Tourtellottee, W. W. 1983 New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann. Neurol.* **13**, 227–231.

Pujol, J., Bello, J., Deus, J., Martí-Vilalta, J. L. & Capdevila, A. 1997 Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* **49**, 1105–1110.

Rao, S. M., Leo, G. J., Bernardin, L. & Unverzagt, F. 1991*a* Cognitive dysfunction in multiple sclerosis: frequency, patterns and prediction. *Neurology* **41**, 685–691.

Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L. & Unverzagt, F. 1991*b* Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* **41**, 692–696.

Reisches, F. M., Baum, K., Brau, H., Hedde, J. P. & Schwindt, G. 1988 Cerebral magnetic resonance imaging findings in multiple sclerosis. *Arch. Neurol.* **45**, 1114–1116.

Revesz, T., Kidd, D., Thompson, A. J., Barnard, R. O. & McDonald, W. I. 1994 A comparison of the pathology of primary and secondary progressive multiple sclerosis. *Brain* **117**, 759–765.

Ron, M. A. & Logsdail, S. J. 1989 Psychiatric morbidity in multiple sclerosis: a clinical and MRI study. *Psychol. Med.* **19**, 887–895.

Ron, M. A., Callanan, M. M. & Warrington, E. K. 1991 Cognitive abnormalities in multiple sclerosis: a psychometric and MRI study. *Psychol. Med.* **21**, 59–68.

Rovaris, M., Filippi, M., Falautano, M., Minicucci, L., Rocca, M. A., Martinelli, V. & Comi, G. 1998 Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology* **50**, 1601–1608.

Rushton, D. 1975 Use of Pulfrich pendulum for detecting abnormal delay in the visual pathway in multiple sclerosis. *Brain* **98**, 283–296.

Ryan, L., Clark, C. M., Klonoff, H., Li, D. & Paty, D. 1996 Patterns of cognitive impairment in relapsing–remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. *Neuropsychology* **10**, 176–193.

Sabatini, U. (and 9 others) 1996 Involvement of the limbic system in multiple sclerosis patients with depressive disorders. *Biol. Psychiatr.* **39**, 970–975.

Sadovnick, A. D., Eisen, K., Ebers, G. C. & Paty, D. W. 1991 Cause of death in patients attending multiple sclerosis clinics. *Neurology* **41**, 1193–1196.

Sadovnick, A. D. (and 13 others) 1996 Depression and multiple sclerosis. *Neurology* **46**, 629–631.

Schiffer, R. B., Wineman, N. M. & Weitcamp, L. R. 1986 Association between bipolar affective disorder and multiple sclerosis. *Am. J. Psychiatr.* **143**, 94–95.

Shibasaki, H., McDonald, W. I. & Kuroiwa, Y. 1981 Racial modification of clinical picture of multiple sclerosis; comparison between British and Japanese patients. *J. Neurol. Sci.* **49**, 253–271.

Sibley, W. A., Bamford, C. R. & Clark, K. 1985 Clinical viral infections and multiple sclerosis. *Lancet* **i**, 1313–1315.

Skegg, K., Corwin, P. A. & Skegg, D. G. C. 1988 How often is multiple sclerosis mistaken for a psychiatric disorder? *Psychol. Med.* **18**, 733–736.

Thompson, A. J., Kermode, A. G., Wicks, D., MacManus, D. G., Kendall, B. E., Kingsley, D. P. E. & McDonald, W. I. 1991 Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann. Neurol.* **29**, 53–62.

Thompson, A. J., Polman, C. H., Miller, D. H., McDonald, W. I., Brochet, B., Filippi, M., Montalban, X. & De Sá, J. 1997 Primary progressive multiple sclerosis. *Brain* **120**, 1085–1096.

Weinshenker, B. G., Bass, B., Rice, G. P. A., Noseworthy, J., Carriere, W., Baskerville, J. & Ebers, G. C. 1989 The natural history of multiple sclerosis: a geographically based study. 1. Clinical course and disability. *Brain* **112**, 133–146.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES