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THE ROYAL SOCIETY

Nuclear magnetic resonance monitoring of treatment and prediction of outcome in multiple sclerosis

David H. Miller* **and Alan J. Thompson**

Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Magnetic resonance (MR) techniques provide an objective, sensitive and quantitative assessment of the evolving pathology in multiple sclerosis. There is an increasing definition of the pathological specificity of newer techniques, and more robust correlations with clinical evolution are emerging. As the pathophysiological basis of *in vivo* nuclear MR signal abnormalities is further elucidated, it is likely that the importance of MR as a tool to monitor new therapies will increase.

Keywords: multiple sclerosis; monitoring treatment; magnetic resonance imaging; predicting outcome

1. INTRODUCTION

Although definitive evaluation of new therapies should be based on clinically meaningful outcomes, there are major difficulties to overcome when conducting treatment trials in multiple sclerosis (MS) with clinical end-points such as relapse rate or progression in disability. The generally slow but unpredictable clinical evolution necessitates large studies (hundreds of patients) of long duration (two to three years), with an active treatment group being compared with a control group. It is thus not surprising that there has been much effort to identify alternative measures of disease activity to monitor treatment efficacy. To be an effective replacement (or 'surrogate', as it is often called) of clinical outcomes the measure of disease activity needs to be objective, sensitive and cost-effective, accurate, and reproducible; most important of all, it should be unambiguously predictive of clinical outcome. This paper reviews the current status of magnetic resonance imaging (MRI) as a treatment monitoring tool, and proposes trial designs using MR outcomes to address specific therapeutic questions.

2. STATUS OF MAGNETIC RESONANCE IMAGING AS A TOOL TO MONITOR TREATMENT

(a) *Objectivity*

Objectivity is difficult to achieve when monitoring clinical outcomes. Blinding may be broken for patients when they experience treatment-related side-effects and for investigators who observe overt side-effects or who unwisely discuss the patient's experiences during the trial. MRI outcomes avoid the bias of unblinding, since the investigator who analyses the scans can be totally separate from the patient. There is no evidence that the placebo effect has a major influence on the amount of MRI activity.

*Author for correspondence.

(b) *Sensitivity*

A sensitive outcome measure will allow treatment effects to be seen more rapidly and in a smaller number of patients than is possible using clinical outcomes; it follows that a sensitive outcome should be cost-effective. In relapsing–remitting (RR) MS, monthly T2-weighted and standard dose ($0.1\,mmol\,kg^{-1}$) gadolinium-enhanced T1-weighted brain MRI reveals about ten active (i.e. new and/or enhancing) lesions for every clinical relapse (Harris *et al.* 1991; Thompson *et al.* 1992; Barkhof *et al.* 1992). Slightly lower levels of activity are found in secondary progressive (SP) MS (Thompson *et al.* 1991; Tubridy *et al.* 1998*b*), but there is much less activity in those with primary progressive (PP) disease (Thompson *et al.* 1991; Kidd *et al.* 1996). Therapy-induced reductions in the number of active lesions have been demonstrated in as few as seven patients with RR or SP MS studied for only six to nine months (Moreau *et al.* 1994). MRI activity varies considerably between and within patients over time. Because interpatient variability is greater that intrapatient, crossover designs are more powerful than parallel group studies. However, the latter provide a more robust assessment of therapeutic effect (McFarland *et al.* 1992; Nauta *et al.* 1994), as the former are more susceptible to the effects of selection bias and regression to the mean. Numerous positive trials using crossover and parallel group designs have been reported (Moreau *et al.* 1994; IFNB Study Group 1995; Jacobs *et al.* 1996; Stone *et al.* 1995; PRISMS 1998; European Study Group 1998; Edan *et al.* 1997; Andersen *et al.* 1996; Karussis *et al.* 1996; Sorensen *et al.* 1998; Durelli *et al.* 1994; Mancardi *et al.* 1998; Tubridy *et al.* 1999) (table 1).

New enhancing lesions are seen twice as often as new T2 lesions on monthly brain MRI in RR or SP MS (Miller *et al.* 1993). The number of enhancing lesions detected is increased by weekly scanning (Lai *et al.* 1996), spinal imaging (Thorpe *et al.* 1996), triple-dose gadolinium ($0.3\,mmol\,kg^{-1}$) (Filippi *et al.* 1996*b*), magnetization transfer (MT) T1-weighted sequences (Silver *et al.* 1997;

Table 1. *Studies showing a reduction in MRI activity in MS with treatment*

therapy	design	effect (%)	reference
β-interferon-1b	parallel group (RR)	60–75	IFNB Study Group (1995)
β-interferon-1b	baseline crossover (RR)	75	Stone *et al.* (1995)
β-interferon-1a	parallel groups (RR)	50	Jacobs *et al.* (1996)
β-interferon-1a	parallel groups (RR)	75	PRISMS (1998)
β-interferon-1b	parallel groups (SP)	*ca.* 75	European Study Group (1998)
campath-1H	baseline crossover (SP)	90	Moreau *et al.* (1994)
mitoxantrone	parallel groups (RR/SP)	80	Edan *et al.* (1997)
linomide	parallel groups (RR)	70	Andersen *et al.* (1996)
linomide	parallel groups (SP)	55	Karussis *et al.* (1996)
intravenous IgG	double crossover (RR)	70	Sorensen *et al.* (1998)
α-interferon	parallel groups (RR)	95	Durelli *et al.* (1994)
copolymer-1	baseline crossover (RR)	60	Mancardi *et al.* (1998)
anti-VLA-4 (very late antigen-4) antibody	parallel groups (RR/SP)	50	Tubridy *et al.* (1999)

Van Waesberghe *et al.* 1997), delayed scanning (Silver *et al.* 1997), and thinner slices (Filippi *et al.* 1996*c*). Of these, the triple dose adds the most: there is a 70% increase in the number of enhancing lesions compared with a single dose (Filippi *et al.* 1996*b*; Silver *et al.* 1997; Van Waesberghe *et al.* 1997), and serial studies have reported a 50% increase in the number of new enhancing lesions, with a smaller sample size needed to show a given treatment effect (Filippi *et al.* 1998*a*).

For unenhanced imaging, strategies which modestly increase sensitivity for small lesions (compared with the standard proton density (PD)/T2-weighted sequence) include two-dimensional and three-dimensional (3D) fast fluid-attenuated inversion recovery (FLAIR) (Filippi *et al.* 1996*a*; Gawne-Cain *et al.* 1997) and higher field scanners, e.g. 4 T (Keiper *et al.* 1996). The value of these approaches in monitoring therapy is not yet defined.

(c) *Accuracy and reproducibility*

An accurate technique should visualize all the macroscopic plaques, and provide a measure of the microscopic lesions that occur in normal-appearing white matter. Post-mortem correlations indicate that conventional T2-weighted imaging is fairly accurate in detecting plaques (Stewart *et al.* 1986; Ormerod *et al.* 1987). However, at the standard 5 mm slice thickness small lesions are undoubtedly missed: in one study, there was a 9% increase in lesion load when slice thickness was reduced to 3 mm (Filippi *et al.* 1995*d*). Fast FLAIR also detects some lesions not seen on T2 images, especially those in a subcortical or cortical location (Filippi *et al.* 1996*a*; Gawne-Cain *et al.* 1997), although it is less sensitive in the posterior fossa and spinal cord (Stevenson *et al.* 1997). Recent work using 3D fast FLAIR shows that there is no further increase in total lesion load when going from 3 mm to 1 mm slice thickness (Molyneaux *et al.* 1998*b*); however, compared with 5 mm thick T2-weighted spin-echo, both 1 mm and 3 mm thick 3D fast FLAIR provided a 30% increase in cerebral lesion volume. Nonetheless, measurement of total T2 lesion load has proven adequate in demonstrating therapeutic effects.

The MRI outcome measure should have a high degree of reproducibility. If not, changes over time might be attributable to measurement error rather than to biological events. Rules have been developed to improve the reproducibility of counting enhancing lesions (Barkhof *et al.* 1997*b*). For T2 lesion load, automated and semi-automated methods are more reproducible than manual lesion outlining (Grimaud *et al.* 1996; Filippi *et al.* 1995*c*; Udupa *et al.* 1997; Molyneaux 1998*a*), but these methods need to be validated for accuracy—failure to do so may give spurious results (Molyneaux *et al.* 1997). Accuracy can be assessed using phantoms of known dimensions (Tofts *et al.* 1997) or by an experienced observer visually assessing the segmented lesion regions.

(d) *Clinical predictive value*

The most essential requirement for a valid MRI outcome measure is that its findings are predictive of future clinical outcome, especially sustained progression in disability. Factors which potentially influence the MR–clinical relationship are now discussed.

(i) *Clinical scales*

Commonly used clinical scales, such as the Kurtzke expanded disability status scale (EDSS), are compromised by subjectivity, poor reproducibility, lack of representation of all facets of functional impairment, and insensitivity to change (Rudick *et al.* 1996; Thompson & Hobart 1998), and such deficiencies should be borne in mind when attempting to correlate clinical and MRI measurements. There is also an obvious limitation when one correlates brain MR findings with a locomotor disability scale that largely reflects spinal cord involvement; moderately better correlations are found with scales of neuropsychological impairment (Rao *et al.* 1989; Ron *et al.* 1991). In summary, an improvement in MR measures should be accompanied by efforts to improve the quality of clinical and neuropsychological scales.

(ii) *Lesion extent*

Established multiple sclerosis

Both cross-sectional and longitudinal studies have reported only a weak correlation between total lesion load (and its change over time) seen on conventional T2-weighted images and disability measured using the EDSS (IFNB Study Group 1995; Thompson *et al.* 1990).

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A cross-sectional study comparing fast FLAIR and T2-weighted images showed similar, modest correlations between lesion load and EDSS (Gawne-Cain *et al.* 1998), with somewhat better correlations in RR than progressive forms of MS. Overall, current evidence in established MS indicates that the total extent of brain lesions correlates only modestly with locomotor disability.

Clinically isolated syndromes

In patients with a clinically isolated syndrome typical of MS, such as optic neuritis, brainstem or spinal cord syndromes, there is a strong correlation between the number of brain white matter lesions on MRI and progression to clinically definite MS in the next one to five years (Beck *et al.* 1993; Morrissey *et al.* 1993; Soderstrom *et al.* 1994; Barkhof *et al.* 1997*a*). At a recent ten-year follow-up, a strong correlation was found between changes in T2 lesion number–load and EDSS in the first five years, but there was a weaker correlation in the second (O'Riordan *et al.* 1998*b*), suggesting that the influence of lesion load as a predictor of disability decreases with increasing disease duration.

(iii) *Lesion site*

Most of the lesions causing locomotor disability are located in the spinal cord or posterior fossa. A higher posterior fossa lesion load has been reported in patients with progressive disease compared with benign MS in some (Koopmans *et al.* 1989; Filippi *et al.* 1995*a*) but not all (Thompson *et al.* 1990) studies. Neither the number nor load of intrinsic focal lesions in the spinal cord correlates with EDSS (Kidd *et al.* 1993). Furthermore, asymptomatic cord lesions have been identified in one-third of patients with clinically isolated optic neuritis (O'Riordan *et al.* 1998*a*). It is thus apparent that patients can have extensive MRI lesions in clinically eloquent pathways without functional consequences. The reasons for this discrepancy are discussed by Smith & McDonald (this issue).

(iv) *The pathological nature of lesions*

The pathological nature of lesions is likely to be a crucial factor in determining their functional effects. Acute MS lesions display inflammation (perivascular lymphocytes, macrophage infiltrates), oedema and active myelin breakdown, and sometimes also reveal evidence of axonal damage (Ferguson *et al.* 1997; Trapp *et al.* 1998; Lassmann, this issue; Anthony, this issue; Perry & Anthony, this issue). Subacute lesions may show variable degrees of remyelination. Chronic plaques are usually completely demyelinated, with marked astrocytic gliosis and a variable degree of axonal loss—the latter is sometimes very marked. Chronic plaques may sometimes exhibit inflammation at their edge.

Inflammation

Inflammation (infiltrates of lymphocytes and/or activated macrophages) correlates well with gadolinium enhancement in both experimental allergic encephalomyelitis (Hawkins *et al.* 1990) and in MS (Katz *et al.* 1993; Nesbit *et al.* 1991; Bruck *et al.* 1997). Enhancement is consistently seen in new brain lesions in RR (Thompson *et al.* 1992) and SP MS (Thompson *et al.* 1991), and usually lasts two to six weeks, similar to the duration of clinical relapses. Enhancing lesions in the brain are more common during relapse than remission (Grossman *et al.* 1986), although the great majority are asymptomatic: enhancing cord lesions are much more likely to result in clinical relapse (Thorpe *et al.* 1996). In acute optic neuritis, enhancement of the symptomatic lesion correlates with acute visual loss and conduction block (reduced amplitude of the visual evoked potential) (Youl *et al.* 1991). Overall, the evidence suggests that gadolinium enhancement is a good surrogate marker for acute relapses. However, in established MS the number of enhancing lesions on short-term MRI studies only modestly predicts the risk for disability in the next one to five years (Smith *et al.* 1993; Giovanonni *et al.* 1997; Losseff *et al.* 1996*a*; Kappos 1999), and other techniques are needed to predict disability better.

Demyelination and axonal loss

These are the major causes of functional impairment in MS. Conduction block results from demyelination, although it is not necessarily permanent as conduction can be restored by the reorganization of sodium channels along the internodal membrane (Moll *et al.* 1991; Smith & McDonald, this issue). Progressive axonal loss is most likely to underlie the irreversible and progressive disabilities so often seen in the later years of the disease. Several MR methods have been proposed to monitor these pathologies, and have shown promise in preliminary studies in correlating rather well with disability and/or clinical course (Arnold *et al.* 1990; Gass *et al.* 1994; Davie *et al.* 1995; Losseff *et al.* 1996*b*, 1997; Truyen *et al.* 1996; Burkhof & Van Walderveen, this issue).

(e) *Magnetization transfer imaging*

This technique examines the pool of protons bound to macromolecules. Normal white matter has a high MT ratio (MTR) because it is highly structured. Protons bound to myelin have a major effect on MTR and a major reduction in this parameter probably indicates demyelination. This is supported by several lines of experimental (Dousset *et al.* 1992, 1995) and clinical (Dousset *et al.* 1997; Silver *et al.* 1996; Thorpe *et al.* 1995) evidence, and measures of functional impairment have been correlated more strongly with MTR than T2 lesion load (Gass *et al.* 1994; Van Buchem *et al.* 1996).

(f) *T1 hypointense lesions*

About 20–30% of lesions seen on T2-weighted scans are hypointense on T1-weighted images (the rest are isointense or slightly hyperintense). One study reported a correlation between change in hypointense lesion load and change in EDSS over three years in SP but not RR MS (Truyen *et al.* 1996). Hypointense lesions have been correlated with axonal loss at post-mortem (Van Walderveen *et al.* 1998).

(g) *Magnetic resonance spectroscopy*

The proton MR spectrum of the normal brain shows a prominent peak due to *N*-acetyl aspartate (NAA). NAA is contained almost exclusively within neurons in the adult brain; a reduction indicates loss or dysfunction of neurons and a persistent reduction in white matter is

expected where there is axonal loss. MR spectroscopy thus has a unique potential to directly monitor axonal loss. A strong inverse correlation exists between cerebellar white matter NAA concentration and the severity of ataxia (Davie *et al.* 1995). In the cerebral hemispheres, lower NAA levels are seen in SP when compared with RR MS (Matthews *et al.* 1996).

(h) *Atrophy*

Atrophy is a likely consequence of axonal or myelin loss. Highly reproducible methods for measuring volumes in the brain and spinal cord have been developed (Losseff *et al.* 1996*b*, 1997), especially based on 3D volume acquisition sequences, and strong correlations have been found between atrophy and disability (Davie *et al.* 1995; Losseff *et al.* 1996*b*, 1997). A correlation between atrophy and reduced NAA concentration in the cerebellum suggests that axonal loss in particular makes an important contribution to atrophy (Davie *et al.* 1995). Measurement of cord volume at the C_2 level is highly sensitive to change, even within one year (Stevenson *et al.* 1998).

(i) *Diffusion tensor imaging*

Using seven-axis diffusion gradients and echo-planar imaging, it is possible to derive images of diffusion anisotropy in white matter tracts, i.e. where higher diffusion rates are seen parallel to the fibre tracts than perpendicular. Loss of anisotropy could therefore be a valuable indicator of loss of structural integrity of fibre tracts and preliminary studies in MS have identified abnormalities in both lesions and normal-appearing white matter (Werring *et al.* 1999*a*).

(j) *'Myelin' imaging: T2 magnetization decay analysis*

A multi-echo train with a short interecho interval allows the determination of multiple tissue water compartments which have different T2 relaxation times. A very short T2 (< 10 ms) is probably due to bound water; in normal white matter this will be mainly myelin-associated water. MS plaques lose the short T2 peak seen in normal white matter (MacKay *et al.* 1994). This method now needs to be studied in a large clinical cohort.

(i) *Normal-appearing white matter*

Microscopic pathology is found in macroscopically normal white matter in MS (Allen & McKeown 1979), and quantitative abnormalities of T1, T2, MTR and NAA have all been reported (Dousset *et al.* 1992; Miller *et al.* 1989; Arnold *et al.* 1992; Davie *et al.* 1997), but their clinical impact is not yet clarified. Reduced NAA in normal-appearing white matter may sometimes be a result of Wallerian degeneration following axonal transection in focal plaques.

(ii) *Cortical pathology and synaptic adaptation*

Cortical synaptic adaptation mechanisms could potentially contribute to remission and recovery in MS, and this mechanism can now be explored using functional MRI (Clanet *et al.* 1996). In a preliminary study of patients who had recovered from an attack of isolated unilateral optic neuritis, abnormal areas of activation well beyond the primary visual cortex were seen in response to stimulation of the previously symptomatic eye (Werring *et al.* 1999*b*).

Cortical plaques, although rarely seen on conventional MRI, are frequently found at post-mortem (Lumsden 1970; Brownell & Hughes 1962; Kidd *et al.* 1999). The functional impact of cortical pathology should be addressed by developing better imaging methods for identifying cortical pathology. Possible approaches include MT–fast FLAIR or a double inversion recovery sequence to suppress cerebrospinal fluid and white matter.

3. SPECIFIC CLINICAL TRIAL DESIGNS

This section reviews a number of specific trial designs. The reader is also referred to several recent reviews which discuss many relevant issues surrounding the use of MR techniques to monitor new treatments (Miller *et al.* 1996, 1998*a*; Evans *et al.* 1997; Filippi *et al.* 1998*b*).

(a) *Optimal MR design in pilot therapeutic trials: safety and efficacy (phase I/II)*

These trials are essentially confined to RR and SP MS, as there is much less MRI activity in the PP group. Monthly T2-weighted and gadolinium-enhanced ($0.1\,\mathrm{mmol\,kg^{-1}}$) brain imaging is usual. In RR MS, a parallel groups design with a placebo arm requires about 2×40 patients to show a 60% reduction in new enhancing lesions over six months (McFarland *et al.* 1992). A one-month run-in scan reduces the sample sizes needed by about 30% (Nauta *et al.* 1994; Tubridy *et al.* 1998*a*). Slightly larger sample sizes are required in SP MS (Arnold *et al.* 1992). Crossover designs are more powerful, because there is less intrapatient than interpatient variability in MRI activity. A single crossover design with a six month run-in followed by six months of treatment requires 10–12 patients to show a 60% reduction in activity (McFarland *et al.* 1992). Double crossover designs are equally powerful, but there needs to be a washout period between the two phases. Single crossover designs may also be contaminated by regression to the mean. If a safe and cheap drug shows only a moderate reduction in activity (e.g. 50%) in a small crossover study, this might be sufficient evidence to justify going straight to a phase III trial. However, if the drug has more side-effects or expense, a parallel group design with the larger sample sizes (e.g. 2×40 for six months) should probably be undertaken first in order to gain more certainty about the MRI effect. It should be remembered that studies of this size will not detect infrequent, severe side-effects.

In pilot studies sample size may be reduced by selecting only those with enhancing lesions during run-in, or by using triple-dose gadolinium—experience with triple-dose gadolinium reveals a 50% increase in new enhancing lesions (Filippi *et al.* 1998*a*), and this approach combined with delayed scanning and MT more than doubles the overall yield of all enhancing lesions (Silver *et al.* 1997).

Early phase I/II MRI studies are important in identifying therapies which are likely to be ineffective (no reduction in MR activity) or which may even be unsafe (increase in MRI activity). Such outcomes should avoid the time, expense and risks of an unnecessary phase III study.

(b) *Optimal MR design in definitive trials (phase III)*

MRI is very useful for two reasons: (i) it provides additional information concerning treatment effect, over and above the primary clinical outcomes (usually disability or relapse rate), and (ii) there is an opportunity to learn about the disease and the measures themselves. The application of multiple MR parameters in large clinical trials now and in the future will also provide insights into the evolving MR–clinical relationship.

T2-weighted brain imaging to measure total lesion load is the simplest sequence to acquire. As a minimum, an entry and exit scan should be obtained; more usually scans are obtained yearly. T2-weighted scans can also be used to count the number of new or enlarging lesions; in a recent large trial in SP MS we found that this outcome was as efficient as T2 lesion volume measurement in demonstrating treatment efficacy and in correlating with changes in disability (Miller *et al.* 1998*b*). Counting new lesions is also a much quicker and more cost-efficient procedure than measuring lesion volume from electronic image data.

Enhanced scanning in a subgroup on a monthly basis throughout several years of the study will help evaluate the efficacy of treatment over time. It is especially relevant to include putative markers of demyelination and axonal loss where possible (e.g. MTR, spectroscopy, atrophy). Their implementation in multicentre trials is more problematic than conventional T2-weighted or gadolinium-enhanced imaging; technical challenges include standardization of acquisition, reproducibility, stability and sensitivity to change (Leary *et al.* 1999). The potential importance of the techniques is their greater apparent predictive value for long-term disability.

(c) *Optimal design in clinically isolated syndrome trials*

This clinical setting is unique in that strong correlations are found between conventional MRI parameters (T2 and enhanced images) and clinical outcome. The presence of T2 MRI abnormalities at presentation with an acute syndrome predicts a greater than 80% chance of relapse leading to a diagnosis of MS in the next ten years (O'Riordan *et al.* 1998*b*); in contrast less than 20% with a normal scan go on to develop MS. The presence of gadolinium-enhancing lesions increases the risk of early conversion to MS (Barkhof *et al.* 1997*a*), as does the occurrence of new lesion activity within three months of presentation (P. Brex, personal communication). Furthermore, T2 lesion load and number changes over the first five years correlate strongly with changes in disability (Morrissey *et al.* 1993; Filippi *et al.* 1994). In trials aimed at delaying the conversion from a clinically isolated syndrome to definite MS, MRI abnormalities should be required as an entry criterion, and serial T2 images should be acquired to measure outcome (along with the primary clinical outcome). Further studies are needed to determine the frequency of abnormalities of putative markers of demyelination and axonal loss in patients with clinically isolated syndromes—our preliminary experience using MR spectroscopy suggests that axonal abnormalities are not yet apparent in the normal-appearing white matter (P. Brex, personal communication).

(d) *Primary progressive multiple sclerosis*

This group has been relatively neglected to date. Problems in performing clinical trials in PP MS are the smaller patient cohort (10% of cases of MS), a relative lack of natural history data on the clinical course, and a typically low brain lesion load on MRI (Thompson *et al.* 1990, 1997). However, recent follow-up of a cohort of 160 patients from six European centres revealed a 5–10% mean increase in T2 lesion load per annum (Stevenson *et al.* 1999), which should be a sufficient magnitude of change against which to demonstrate a treatment effect. The MR protocol should consist of T2-weighted imaging, and fast FLAIR imaging may be useful in addition (fast FLAIR detects an additional 20% of lesions in the subcortical region in PP MS (Gawne-Cain *et al.* 1997)). Atrophy measures show particular promise (Stevenson *et al.* 1998). It is therefore of importance to collect putative markers of demyelination and axonal loss, given their potential to predict disability more strongly. Gadolinium enhancement shows few focal enhancing lesions in this subgroup (Silver *et al.* 1997; Filippi *et al.* 1995*b*).

(e) *Treating acute relapses*

Here, MRI techniques may be employed to monitor the effect of treatment on the evolving pathology of the symptomatic lesion. Potential MRI outcomes include the total extent of the residual T2-weighted lesion, the duration and intensity of gadolinium enhancement of the symptomatic lesion, or the pathological severity of the residual lesion (by using putative markers of demyelination and axonal loss). The latter methods are more difficult to apply in the optic nerve and spinal cord, the site of many of the lesions causing acute relapse. Nevertheless, lesion extent can be determined in the optic nerve, and this site allows excellent clinical and electrophysiological correlations of the evolving MRI lesion. It has been shown that poor visual recovery in optic neuritis is associated with longer optic nerve lesions (Miller *et al.* 1988), and that intravenous methyl prednisolone does not modify the evolution or final length of the MRI lesion (Kapoor *et al.* 1998).

(f) *Treatment to enable repair and remyelination*

Repair and remyelination might be evaluated by monitoring reversal of abnormalities seen with the putative MR markers of demyelination. For example, reversal of MTR abnormalities, as often occurs in acute lesions (Lai *et al.* 1997; Dousset *et al.* 1998), could be due at least in part to remyelination. MR–pathological studies are needed to investigate this hypothesis.

4. OTHER ISSUES

It is important to use adequate quality assurance procedures in longitudinal studies. The methods of statistical analysis are also crucial. These are discussed in a recent review based on the proceedings of an international workshop on MR in MS (Thompson *et al.* 1997). There is a need for further work which directly correlates MR findings with pathology in experimental and human inflammatory–demyelinating diseases. Much progress is still possible using MR technology, e.g. improved resolution with 3D acquisition and higher-field scanners; better

pathological specificity with 'myelin' imaging; new image analysis methods to improve the speed, accuracy and reproducibility of measurements. The detection of diffuse signal abnormality in the spinal cord in progressive forms of MS using a PD sequence (Lycklama *et al.* 1997) emphasizes the need to apply other quantitative MR techniques to characterize more fully the functionally important intrinsic cord pathology.

Above all, it must be emphasized that to be meaningful any new MRI outcome measure should be validated by demonstrating an unambiguous correlation with a clinically relevant measurement of functional status.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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