Brain (1998), **121,** 3–24

REVIEW ARTICLE

The role of magnetic resonance techniques in understanding and managing multiple sclerosis

D. H. Miller,[1] R. I. Grossman,[2] S. C. Reingold[3] and H. F. McFarland[4]

[1]*Institute of Neurology, London, UK,* [2]*Hospital of the University of Pennsylvania, Philadelphia,* [3]*National Multiple Sclerosis Society, New York, and* [4]*National Institutes of Health, Bethesda, USA*

Correspondence to: Professor D. H. Miller, Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1 3BG, UK

Summary

Magnetic resonance (MR) techniques have had a major impact in the last 10–15 years in understanding and managing multiple sclerosis. This review summarizes the current uses of MR in multiple sclerosis, based on the proceedings of a recent international workshop, under four headings: (i) technical issues; (ii) role in diagnosis; (iii) natural history studies in understanding the disease; (iv) application in clinical trials. The theory and methodology of relevant technical issues is outlined, in order to provide a framework with which to understand the potential and limitations of MR in addressing biological and clinical questions in multiple sclerosis. The principles underlying signal-to-noise and contrast-to-noise ratio are discussed, along with the techniques and clinical results for conventional and fast spin echo T_2-weighted imaging, fluid-attenuated inversion recovery, detection of blood–brain barrier break down and hypointense lesions on T_1-weighted images, magnetization transfer, T_2 decay-curve analysis, MR spectroscopy, spinal cord imaging, diffusion imaging, and quantification of lesion load and atrophy. MRI has an extremely valuable role in confirming the clinical diagnosis of multiple sclerosis. T_2-weighted brain imaging remains the standard diagnostic tool, but in some instances it is usefully complemented with gadolinium enhancement and spinal imaging. The caveat that the diagnosis of multiple sclerosis remains primarily a clinical one cannot be over-emphasized. Serial MRI studies have added much to our understanding of the natural history and pathophysiology of the disease. Blood–brain barrier breakdown is a consistent early feature of new lesion development in relapsing–remitting and secondary progressive multiple sclerosis, and this usually correlates with active inflammation and myelin breakdown. A number of the acute MR changes are reversible, but chronic persistent abnormalities in a number of MR parameters, such as reduced N*-acetyl aspartate, low magnetization transfer ratios, atrophy and T_1-hypointensity, suggest the presence of demyelination and/or axonal degeneration in many chronic lesions. The presence and extent of T_2-weighted MRI abnormalities at first presentation with a clinically isolated syndrome suggestive of demyelination strongly predicts the risk of developing clinically definite multiple sclerosis in the next few years. In established multiple sclerosis, however, the correlations between T_2 abnormalities and disability are modest. This poor relationship partly relates to the discrepancy between lesion site and function in attempting to correlate locomotor disability with brain MRI findings. However, the correlations between brain lesion load and cognitive dysfunction in multiple sclerosis, whilst more evident, are still modest. A more important limitation is the low pathological specificity of abnormalities seen on T_2-weighted images. Stronger correlations have been found between disability and new putative MR markers for demyelination and/or axonal degeneration. Serial studies using multiple MR techniques are now needed to further clarify pathophysiological mechanisms in multiple sclerosis. Serial MR has become an important tool in monitoring treatment efficacy. It provides data which can be readily analysed in a blinded fashion and which directly inspects the pathological evolution; it also enables a rapid and sensitive measure of treatment outcome in early relapsing–remitting and secondary progressive disease. Because of the modest clinical correlations it is, however, still appropriate that the definitive determinant of treatment efficacy remains a clinical one. Further work is needed to address issues of quality control in serial studies, statistical calculation of appropriate sample sizes, and optimization of the nature and frequency of MR outcomes measured.*

Keywords: magnetic resonance; multiple sclerosis

Abbreviations: BBB = blood–brain barrier; CSE = conventional spin echo; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin echo; MR = magnetic resonance; MRS = magnetic resonance spectroscopy; MT = magnetization transfer; MTR = magnetization transfer ratio; NAA = *N*-acetylaspartate; PD = proton density; SNR = signal-to-noise ratio; TE = echo time; TGSE = turbo gradient spin echo; TR = repetition time

Introduction

The last several years have seen a rapidly increasing evolution of magnetic resonance (MR) technology and an increased focus on its application to multiple sclerosis. A 1994 consensus conference on outcomes assessment in multiple sclerosis clinical trials held in Charleston, South Carolina (Whitaker *et al*., 1995) focused attention on MR technology in the setting of experimental trials in multiple sclerosis. A recent international workshop on the role of MR technology in understanding and managing multiple sclerosis (Oxford, UK, January 15–19, 1997; see Acknowledgements), as well as several recent focused working groups on use of MR in clinical trials (Miller *et al*., 1996) and on quantification of MR (Evans *et al*., 1997), point to the advances and the continuing shortfalls of current technologies and serve as the framework for this comprehensive review.

In a disease with a high degree of variability of clinical signs and symptoms over time and between individuals, and with no current adequate biological markers of disease progression, MR techniques provide a direct indication of disease pathology. MR has an established role as an aid in the diagnosis of multiple sclerosis. Serial MR studies have an important role in understanding the disease and monitoring its treatment.

In spite of the ability to follow at least some aspects of the evolution of the multiple sclerosis lesion with a battery of MR tools, problems still remain. Most importantly, information on MR imaging remains difficult to correlate with details of pathology and with the clinical status in individual patients. As early as 1868, Charcot related that significant CNS pathology could be present in the absence of clinical signs and symptoms (Charcot, 1868). Though demyelination, the characteristic pathological feature of multiple sclerosis, produces conduction block (McDonald, 1963; McDonald and Sears, 1970) which is the principal mechanism for functional loss, it does not necessarily or even usually lead to permanent loss of function. Recovery of function is possible in multiple sclerosis, usually within weeks of an initial demyelinating event, most likely as a consequence of proliferation and spread of sodium channels (Moll *et al*., 1991). Remyelination undoubtedly occurs and is occasionally extensive at post-mortem, though more commonly it is scanty and confined to the edges of lesions (Prineas and Connell, 1979; Prineas *et al*., 1993). It is not, however, a prerequisite for recovery of function, and in adults it is exceptional for it to be extensive enough to restore normal latencies to evoked potentials (Jones *et al*., 1993).

Gliosis occurs after demyelination (as after many other pathological processes), but its relationship to axonal function is problematical (McDonald, 1997). Certainly, gliosis at sites of demyelination, as indicated by increased signal on proton density (PD) or T_2-weighted images, is compatible with nerve conduction which, though slow, is often associated with virtually normal clinical function. The optic nerve affords a good example (Miller *et al*., 1988*a*).

An important feature of many ‘old’ lesions at post-mortem is axonal loss. It is likely that this makes an important contribution to the irrecoverable deficit which develops in most patients later in the course of the disease (Davie *et al*., 1995); the contribution of secondary failure of the repair mechanisms in persistently demyelinated axons remains to be determined. Evolving MR methodologies which may have greater pathological specificity, and their correlation with clinical change in disease, may well lead to improved understanding of the role of MR as a surrogate marker for multiple sclerosis disease activity.

In the recent international MR workshop held in Oxford, UK, four aspects of the use of MR in multiple sclerosis were examined: (i) technical issues; (ii) the role in diagnosis; (iii) natural history studies and their implications for understanding the disease; (iv) application in therapeutic trials. This paper provides an examination of our current understanding of these areas, as reflected in the workshop discussion.

1. MR: technical issues

Background

MRI of multiple sclerosis has rapidly evolved over the past 15 years. It now plays a pivotal role both in the diagnosis of multiple sclerosis and as a surrogate marker of drug efficacy in treatment trials. In addition to conventional spin echo (CSE) imaging, newer techniques have emerged that promise to increase both our sensitivity and specificity with respect to pathology. In considering newer techniques it is important to appreciate the underlying physical principles that guide imaging and to understand the strengths and weaknesses of each technique. Two general aspects of imaging require special note; time required for the study and the contrast-to-noise ratio which influences the detectability of small lesions.

The time it takes to perform a conventional two-dimensional Fourier transform MR scan is given by: scan time = repetion time interval $\times$ the number of phase encodings $\times$ the number of excitations.

As interest turns to thinner slice thickness it should be

noted that imaging time is the major trade-off when choosing to decrease slice thickness, and reduction in slice thickness by half decreases the signal-to-noise by half. To maintain the same signal-to-noise (in this case) requires doubling of the imaging time.

The detection of a multiple sclerosis lesion using MR is primarily related to the contrast-to-noise ratio that reflects the relative differences in signal intensity between the region-of-interest and the background. If a lesion occupies an entire voxel, its detectability is related primarily to its contrast (against neighbouring voxels). In cases where the lesion fills less than the whole voxel, it is both the percentage of the voxel filled by the lesion, as well as the inherent contrast of the lesion, that determines its detectability. Thus, the smaller the lesion, the higher the contrast-to-noise necessary. Furthermore, variability of volumetric measurement increases as tissue contrast decreases.

Signal-to-noise ratio (SNR), i.e. the mean intensity within a region-of-interest (signal) divided by the standard deviation in the background containing only noise, varies linearly with image voxel size. The larger the voxel, the greater the SNR, while the thinner the slice thickness the lower the SNR. In general signal intensity increases with field strength.

To get comparable signal-to-noise to a 1.5-T magnet (standard high field magnets) on magnets of field strength below 1.5 T, at similar imaging times, generally requires an increase in voxel size. Resolution, on the other hand, increases at the expense of both the SNR and image acquisition time.

The trade-offs in imaging multiple sclerosis lesions are thus straightforward. To detect smaller lesions thinner slices are needed, however, such slices have lower signal-to-noise because of their decreased voxel size.

Techniques for T_2-weighted imaging

Conventional spin echo (CSE) imaging

The CSE pulse sequence has been utilized for most multiple sclerosis clinical trials. The typical pulse sequence used creates two images per repetition time (TR), one with a short echo time (TE) and one with a long TE. These are referred to as PD-weighted and T_2-weighted images, respectively. The long TR minimizes (but does not eliminate) the T_1 effects, so the term 'weighted' is affixed to the type of contrast that dominates the image. For any TR, T_2-weighting increases as TE increases.

K-space is where the raw data of spatially encoded MR signals, collected during the application of the frequency encoding gradient, are placed. Each point in *k*-space contributes to the entire image. In CSE images one 'line' of *k*-space is encoded per TR interval, and the pulse sequence is repeated 128 or 256 times (phase encodings) per image. For each line of *k*-space, the phase encoding gradient amplitude is incremented.

The central lines of *k*-space are responsible for the majority of signal in the image, whereas the outer lines of *k*-space are responsible for the spatial resolution. In CSE MR, phase encoding would be repeated 128 or 256 (size of the matrix, i.e. number of phase encodings) times per TR interval to fill *k*-space. This results in significant time to complete the scan, taking ~9–12 min for a conventional T_2-weighted whole brain examination.

On PD/T_2-weighted images, the multiple sclerosis lesion demonstrates high intensity while background white matter is generally dark. The sequence is robust and easy to apply across centres, however, it is relatively slow. Lesions adjacent to CSF (cortex/subcortical and periventricular regions) may lack conspicuity.

Fast spin echo (FSE) imaging

With FSE imaging, multiple phase encodings are performed in each TR and multiple echoes per TR are acquired. Thus, instead of one line of *k*-space per TR interval, from two to $\geqslant$16 lines of *k*-space are encoded per TR. The number of echoes applied per TR is termed the echo train length and the time between each echo is the echo space. The acquisition of multiple lines of *k*-space per TR has some very important effects. Imaging is faster by a factor in direct proportion to the number of echoes collected. If a conventional scan is 8 min and eight echoes are collected, the FSE scan will be 1 min. Since all the echoes during a TR interval contribute to the signal instead of a single TE, we have the combination of these echoes termed an effective TE. Here the effective TE is determined by the echo that has the lowest phase encoding gradient (central line of *k*-space).

Comparisons between CSE and FSE demonstrate distinctions, including fat generally being bright on T_2 FSE and dark on CSE. FSE and CSE images produce quantitatively equivalent images with respect to detection of high intensity lesions (Norbash *et al*., 1992; Thorpe *et al*., 1994). An important advantage for the FSE sequence in multiple sclerosis is the ability to produce thin contiguous imaging sections with high signal-to-noise and contrast-to-noise in times similar to those used for thicker section CSE images, thus decreasing lesion volume averaging. A variant of the FSE pulse sequence is the use of gradient echoes (those echoes obtained without the 180° refocusing pulse) in addition to spin echoes to fill *k*-space, i.e. turbo gradient spin echoes (TGSEs).

Imaging must be viewed as a continuum. From the slowest to fastest, sequences include (i) CSE with one echo per TR, (ii) FSE with multiple echoes per TR (FSE), (iii) TGSE and (iv) echo planar imaging, where multiple echoes are formed using magnetic field gradient methods. Echo planar imaging can produce images in $\leqslant$100 ms. The penalty of such rapid sequences is a lower SNR.

Fluid-attenuated inversion recovery (FLAIR) imaging

FLAIR imaging is a recently introduced pulse sequence that yields heavily T_2-weighted images in which CSF is nulled

(De Coene *et al*., 1992). The technique couples an inversion pulse with a long inversion time to a long TE readout. FLAIR images have the ability to increase the conspicuity of lesions that are at the interface between brain and CSF. Cortical/subcortical lesions are generally difficult to visualize with CSE imaging because of the lack of contrast between high intensity cortex and high intensity CSF. This is also true for periventricular lesions and adjacent brain. The methodology is potentially useful for multiple sclerosis lesions as it increases the number of lesions visualized (White *et al*., 1992; De Coene *et al*., 1993). To speed up this process the inverting pulse can be combined with a FSE pulse sequence, termed fast FLAIR, and can perform 36 slices of 5-mm thickness in just over 5 min. This sequence demonstrated improvements in lesion detectability, lesion conspicuity, and lesion-to-CSF contrast compared with CSE imaging (Rydberg *et al*., 1994).

3D data sets

The ability to obtain thin slices or acquire 3D data sets enables reformatting of images in any plane. Thus images acquired in the axial plane may be reformatted in the sagittal plane to detect disease at the callosal–septal interface. Another advantage of the 3D data set are comparisons, after registration of longitudinal images, used to reveal subtle changes in lesions over time. A third advantage is higher SNR. Both 3D FSE and fast FLAIR sequences have recently been developed (Barker *et al*., 1997); their role in multiple sclerosis is not yet determined

Comparative imaging results

The sensitivity of CSE, FSE, fast-FLAIR and TGSE have been evaluated semi-quantitatively according to size and site by two groups, with CSE as the 'gold standard' (Filippi *et al*., 1996*a*; Rovaris *et al*., 1997*a*). The results indicated the following. FSE detected 16% more lesions than CSE most of which were found in the cortical/subcortical area. Fast-FLAIR detected 28% more lesions than CSE with the difference again in the cortical/subcortical area; fewer lesions were detected in the posterior fossa. CSE detected 22% more lesions than TGSE. Comparison of fast-FLAIR and FSE demonstrated no significant differences in lesion detection. The conclusion from this data was that FSE or fast-FLAIR could be used in place of CSE, and indeed, because of their speed and increased sensitivity to lesions, they were preferable to CSE for imaging multiple sclerosis. Another advantage of fast-FLAIR is that it may be easier to analyse with contour plot methodology because of the increased conspicuity between lesion and brain/CSF. However, fast-FLAIR did not detect as many lesions, when compared with FSE, in the posterior fossa and spinal cord which are important sites that relate to disability (Filippi *et al*., 1996*e*; Gawne-Cain *et al*., 1997; Stevenson *et al*., 1997). TGSE was inferior to the other sequences but could serve a useful role when reduced examination time is required for patients unable to tolerate a standard MR examination.

Studies have also been performed evaluating the effect of particular pulse sequences on the reproducibility of volumetric measurements using a contour plotting technique (Plummer, 1992). FSE volumes were slightly but significantly smaller than CSE and the reproducibility was very good for both sequences (Rovaris *et al*., 1997*b*).

Imaging techniques for enhancing lesions

The opening of the blood–brain barrier (BBB) may be the earliest event in the development of a multiple sclerosis lesion. Gadolinium chelates, in combination with T_1-weighted images, are sensitive markers of this abnormality. Enhancement is dependent upon the presence of a 'leaky' BBB, the ability of contrast to reach the region, the concentration of the contrast bolus, the timing of the scan in relation to the contrast injection, and the exact MR pulse sequence. A triple dose of gadolinium (0.3 mmol/kg) or a single dose (0.1 mmol/kg) in combination with a preparation pulse (magnetization transfer pulse) that suppresses normal brain, but not enhancement, has been reported to increase the number of detectable lesions in relapsing–remitting and secondary progressive disease (Filippi *et al*., 1996*b*; Silver *et al*., 1997*a*), but not appreciably in primary progressive disease (Filippi *et al*., 1995*a*; Silver *et al*., 1997*a*). Delayed imaging (30–60 min following injection) can also increase the detection of enhancing lesions (Filippi *et al*., 1996*c*). All of these measures, however, have a price. Triple-dose studies are more expensive, there are more false positive lesions (i.e. small vessels) and/or flow artifacts (i.e. around the brainstem and posterior fossa), and delaying scanning interferes with patient throughput. Additionally, the magnetization transfer pulse can produce images that reveal non-enhancing multiple sclerosis lesions to be high intensity and potentially mistaken for contrast-enhancing lesions. It is necessary to perform a precontrast T_1-weighted magnetization transfer image and compare it with the post-contrast image if the use of magnetization transfer is implemented.

Enhancement is more sensitive than either clinical examination or T_2-weighted images in detecting disease activity (Miller *et al*., 1993). This feature enables detection of treatment effects in smaller patient cohorts over shorter time periods (Miller *et al*., 1996). Triple dose appears to be the most sensitive method for increasing post-gadolinium lesion detection by 50–70% (Filippi *et al*., 1997*a*). This also appears to be the case for detection of spinal lesions in multiple sclerosis (Filippi *et al*., 1997*b*). Enhancement is both technique- and dose-related. This impacts on the prescription of imaging protocols in treatment trials and must be accounted for in the evaluation of data from different reports.

Magnetization transfer

Macromolecular protons, i.e. those associated with structural components of brain tissue including myelin have extremely

short relaxation times (T_2s) thus rendering them MR 'invisible'. By applying a radiofrequency saturation pulse 'off' the resonance of free water, these protons can be indirectly imaged. The protons, either by spin-exchange or cross-relaxation, produce decreased intensity on the image. The contrast based upon this process is termed magnetization transfer (MT) contrast and reflects the concentration of macromolecular protons. Regions with the greatest decreased intensity following an off-resonance saturation pulse would have more MT. Multiple sclerosis lesions in which there is either dilution of macromolecular protons (oedema) or loss of structure (demyelination) would exhibit less MT. A quantitative measurement of this effect is termed the magnetization transfer ratio (MTR). This is obtained by acquiring two sets of MR images, one with MT saturation pulses, the other a control image without saturation pulses, but with otherwise identical acquisition parameters. This enables the calculation of the effect of the MT saturation, i.e. the MTR, in a region-of-interest through the use of the following equation.

$$\mathrm{MTR} = (M_o - M_s)/M_o$$

where M_o represents the average pixel intensity in the region when the saturation pulses are off, and M_s the corresponding intensity with MT saturation. Thus, MTR represents the fractional signal loss due to the complete or partial saturation of the bound proton pool, and ranges from near zero in blood and CSF to $\geqslant$50% in tissue that contains a high proportion of poorly mobile macromolecules, such as muscle.

MTR has been found to be highly reproducible in studies of normal and diseased tissue, although the measured MTR is dependent upon the experimental parameters imposed. It depends on the concentration of macromolecules, surface chemistry and biophysical dynamics of macromolecules (Wolff and Balaban, 1994). There is evidence that the MT effect in white matter is secondary to myelin (Fralix *et al*., 1991). MTR may be correlated with the extent of tissue abnormality in multiple sclerosis lesions, offering the potential of increased sensitivity and specificity for MR studies of white matter disease or monitoring therapeutic effects in clinical trials. It has been correlated with oedematous lesions in experimental allergic encephalomyelitis, multiple sclerosis lesions, abnormalities in normal-appearing white matter, hypointense T_1-weighted lesions (so-called 'black holes'), wallerian degeneration, magnetic resonance spectroscopy (MRS), enhancement patterns in multiple sclerosis and other diseases (Dousset *et al*., 1992; Boorstein *et al*., 1994; Gass *et al*., 1994; Hiehle *et al*., 1994, 1995; Lexa *et al*., 1994; Loevner *et al*., 1995*a*, *b*; van Walderveen *et al*., 1995; Hirsch *et al*., 1996; Kimura *et al*., 1996; Truyen *et al*., 1996).

The variation of MT effect with saturation offset-frequency at constant saturation power is termed the *Z*-spectrum. Analysis of the *Z*-spectrum can help determine the intrinsic relaxation and exchange parameters in a particular tissue and perhaps lead to a different type of image based upon MT.

There are some problems associated with MT. It is not an absolute measure, rather it is highly dependent upon the chosen parameters, including the frequency offset and the effective power of the saturating radio-frequency pulse. It is also affected by patient motion. Nevertheless, it remains within centres a highly reproducible measure that can be sensitive to changes in macromolecular structure. Progress is also being made towards the implementation of a 'uniform' MT sequence for multi-centre studies (Berry *et al*., 1996), a prerequisite for large clinical trials in multiple sclerosis.

Region-of-interest analysis is performed when a cursor is placed over a particular region and the mean MTR in that region is measured. The method is useful for detection of MTR in the region sampled by the region-of-interest but it falls short for appreciating the total burden of abnormality, because of finite region-of-interest samples. A method in which data are presented as 3D MTR histograms provides whole brain quantitative MTR data. Comparison of multiple sclerosis patients and control subjects revealed a single peak located along the same *x*-axis with the height of this peak considerably lower for patients than for control subjects (van Buchem *et al*., 1996*a*). The peak height of the histogram reflects the residual amount of normal tissue, and thus inversely reflects the total lesion burden which consists of both T_2 lesion volume and pixels in the normal-appearing white matter that have abnormal MTR. Using this technique 44 untreated multiple sclerosis patients were analysed with peak height of the histogram correlating significantly with disease duration, the Expanded Disability Status Scale (EDSS), Ambulation Index and neuropsychological tests (van Buchem *et al*., 1996*b*). This methodology is fast, sensitive to lesion heterogeneity, and not subject to observer bias. It has the potential for determining effects of drug treatments on both macroscopic lesions and occult lesions not demonstrated by conventional imaging.

Hypointense T_1 lesions ('black holes')

Hypointense T_1 abnormalities were first noted by Uhlenbrock *et al.* (1989) who found that they were more common in multiple sclerosis than in subcortical arteriosclerotic encephalopathy. The pathological substrate for hypointensity is uncertain, and may depend in part on the definition of hypointensity which is applied. Oedematous lesions can appear as hypointensities, and this may contribute to a reversible hypointensity in acute lesions. Preliminary histological examination of chronic lesions appears to reveal a correlation between the degree of hypointensity on T_1-weighted images and 'matrix' destruction and loss of axons (van Walderveen *et al*., 1996). Hypointense T_1-weighted lesions thus may be more harmful than lesions only noted on T_2-weighted images. Change in T_1-weighted lesion load has correlated strongly with change in EDSS over a 3-year period in secondary progressive but not relapsing–remitting multiple sclerosis (Truyen *et al*., 1996). Additionally, secondary progressive multiple sclerosis had a

larger percentage of hypointense T_1-weighted lesions associated with T_2 high intensity abnormalities, suggesting a possible failure of reparative processes. It has also been found that hypointensity on T_1-weighted images correlates with lower MTRs (Hiehle *et al*., 1995; Loevner *et al*., 1995*a*).

The measurement of T_1-weighted 'black holes' must be normalized so that the most significant hypointense lesions are quantified. Such normalization (e.g. to white matter, grey matter or CSF) would enable comparison of results from different centres. In addition, the pulse sequence must be standardized too, and it is important to consider whether the hypointensity is assessed before or after enhancement. Nevertheless, assessment of black holes appears to provide more accurate correlations with clinical markers of disability than standard T_2 quantitative data.

T_2 decay curve analysis

In brain tissue the T_2 decay curve is multi-exponential. Using statistical methodology the T_2 components of the decay curve can be extracted. This method may aid in increasing the specificity of high intensity abnormalities in multiple sclerosis. This requires multi-parametric fitting of the T_2 decay curve and has been proposed as a method to characterize tissue (Gersonde *et al*., 1985). The technique generates $\geqslant$32 echoes from a single slice (Poon and Henkelman, 1992). Multi-exponential analysis programs can convert decay curves into distributions of T_2 components. A plot of T_2 versus amplitude contains several peaks corresponding to different tissue water components and is thought to reflect the relative molecular compartmentalization of the protons (i.e. water with oedema, inflammation, gliosis, axonal loss and demyelination) (Mulkern *et al*., 1989; Armspach *et al*., 1991; Rumbach *et al*., 1991). Normal CNS exhibits three regions on this plot: a minor peak at T_2 = 15–30 ms, a major peak between 70 and 100 ms and another peak with $T_2 > 2$ s (Menon *et al*., 1991). The peak associated with the longest T_2 is assigned to CSF. The major peak consists of intra- and extra-cellular water. The short T_2 peak has been assigned to water compartmentalized between myelin bilayers (MacKay *et al*., 1994). It is possible thus to visualize water with a short T_2 in so-called myelin images. This short T_2 peak is often absent in multiple sclerosis lesions and it is hypothesized that this could be a useful marker of myelin. The issue is to determine if a correlation exists between individual patterns of relaxation times and histopathology. Many reports have correlated various long T_2 relaxation times with particular histopathology (300–500 ms with vasogenic edema; $<$ 300 ms with gliotic lesions) (Barnes *et al*., 1986, 1988; Armspach *et al*., 1991; Rumbach *et al*., 1991). The T_2 decay curve of normal white matter appears to best fit a monoexponential curve, whereas that of visible lesions best fits a biexponential curve (Larsson *et al*., 1988), although exceptions occur (Kidd *et al*., 1997). Such analysis can also be performed in normal-appearing white matter, and has been reported to be slightly abnormal (Armspach *et al*., 1991). T_2 decay curve analysis offers another perspective perhaps with increased specificity regarding multiple sclerosis lesions.

MRS: theory and practice

Proton MRS offers another window on the pathological processes in multiple sclerosis (Richards, 1991). Using TEs of 136 or 272 ms ('long TEs'), four major resonances are detected: choline-containing compounds, creatine/phosphocreatine, *N*-acetylaspartate (NAA) and lactate. Other peaks, best observed using short TEs and described in pathological conditions, include the methyl groups of lipids and other compounds including myo-inositol and unidentified 'marker peaks' (Wolinsky *et al*., 1990; Grossman *et al*., 1992; Davie *et al*., 1994; Hirsch *et al*., 1996).

NAA is a neuronal marker found uniquely in mature brains. Any disease process that results in neuronal loss is associated with decreased levels of NAA (Simmons *et al*., 1991). Acute multiple sclerosis lesions may demonstrate increased choline-containing compounds, which result either from the release of choline-containing membrane lipids during active myelin breakdown or from inflammation (Brenner *et al*., 1993), and/or increased lactate, possibly from inflammation. On short TE MRS, abnormally elevated lipid and myo-inositol peaks may be observed. Over time choline-containing compounds and lactate may return to normal but NAA does not recover fully, although it displays some reversibility (Davie *et al*., 1994).

NAA can be demonstrated to be decreased beyond the borders of the plaque and thus may be an index of overall disease burden (Arnold *et al*., 1992). NAA has also been observed to be decreased in normal-appearing white matter to a greater degree in secondary progressive than in relapsing–remitting multiple sclerosis (D. Arnold, workshop proceedings). Axonal pathology has been linked with axonal function, and thus decreased NAA has been correlated with disability. This has been reported in four patients with single large multiple sclerosis lesions, whereas NAA was also reported to increase as disability improved (De Stefano *et al*., 1995). The concentration of NAA in cerebellar white matter has been strongly correlated with the degree of ataxia on Kurtzke's cerebellar functional system (Davie *et al*., 1995). The exact role that MRS can play in elucidating pathological processes involved in multiple sclerosis is still being clarified. It has the potential of detecting axonal damage as well as other stages of the pathological process in multiple sclerosis. It can provide insight into the mechanisms of functional impairment and perhaps serve as a monitor of therapeutic efficacy, although compared with a number of other MR parameters, quantitative serial MR spectroscopy is potentially more limited by SNR, resolution, reproducibility and sensitivity to change.

Spinal cord imaging: theory and practice

Spinal cord imaging has improved considerably with the advent of phased array coils and FSE pulse sequences. The

lack of spinal cord imaging data has been one possible explanation for the relatively weak correlation between T_2 lesion load and disability measurements. In patients presenting with a clinical picture compatible with multiple sclerosis but normal brain MR, spinal cord imaging has proven to be diagnostically important (Thorpe *et al*., 1996*a*). Alternatively, patients presenting with a spinal cord lesion and suggestive symptoms of multiple sclerosis deserve to have their brain studied. Asymptomatic spinal cord lesions has been reported in ~30% of patients presenting with clinically isolated syndromes suggestive of multiple sclerosis (O'Riordan *et al*., 1996*a*). Theoretically fast FLAIR would appear to be advantageous by creating T_2-weighted contrast with dark CSF; however, results thus far have been disappointing (Filippi *et al*., 1996*e*; Stevenson *et al*., 1997; Kieper *et al*., 1997).

High intensity lesions on T_2-weighted images of the spinal cord are equally distributed among all clinical subgroups and do not correlate with disability (Kidd *et al*., 1993). Additionally, serial studies demonstrate few new cord lesions but a third of those that occur are associated with clinical symptoms (Kidd *et al*., 1996; Thorpe *et al*., 1996*b*). Another approach has been to measure the area of the spinal cord on heavily T_1-weighted images at the C2 level. This has been reported to have a strong and graded relationship between cord atrophy and disability ($r = -0.7$, $P < 0.001$) (Losseff *et al*., 1996*a*). New techniques including MT imaging have been applied to the spinal cord with significant differences reported between patients and control subjects (Silver *et al*., 1997*b*). Exactly where spinal cord imaging fits into clinical trials remains to be determined. There is little doubt of its importance in understanding the disease given the potential to directly monitor much of the disabling pathology in multiple sclerosis.

Diffusion imaging: theory and practice

Diffusion-weighted imaging is a technique that is based upon the microvascular water environment and is sensitive to translation of water molecules over short distances. There are several interesting parameters that can be measured by MR diffusion techniques. Diffusion-weighted imaging employs a pair of magnetic field gradient pulses placed symmetrically around a 180° refocusing pulse, to dephase and rephase static water protons. Diffusing water molecules are dephased resulting in signal loss. Changing the time and amplitude of the gradient pulse (*b*-value) alters the sensitivity to diffusion and enables calculation of an 'apparent' diffusion coefficient since the presence of permeable or nonpermeable barriers hinder the free motion of water (Le Bihan *et al*., 1992). Destruction of the barriers, or changes to the geometry or permeability of barriers lead to changes in the apparent diffusion coefficient. Preliminary reports indicate that the apparent diffusion coefficient is higher in multiple sclerosis lesions than in normal white matter (Horsfield *et al*., 1996). It has been hypothesized that inflammation leads to a decrease in the apparent diffusion coefficient with little loss of tissue anisotropy while axonal loss leads to loss of anisotropy and an increase in the apparent diffusion coefficient. Gliosis may decrease the apparent diffusion coefficient without anisotropy. Presently implementation of this methodology is technically challenging and has not been studied extensively in multiple sclerosis. It remains a formative technique that merits further investigation.

Quantitative techniques

Quantitative data in multiple sclerosis is critical both in understanding the natural history of the disease and in monitoring therapeutic effects. In any evaluation one must appreciate the precision of the method, i.e. how reproducible it is, for an individual observer to replicate measurements and how good multiple observers are at reproducing the same data. Accuracy measures how the quantification agrees with the truth. There are several issues with regard to computerized methods for multiple sclerosis lesion quantification. These can be divided into three categories: recognition, delineation and efficiency. Recognition is the process of determining and distinguishing a specific object from other structures. Delineation defines the extent of the object. Efficiency represents how practical the method is. This takes into account the human time and computational resources necessary to provide the data in a timely fashion—a highly relevant consideration when dealing with the vast datasets during large multi-centre clinical trials. The perfect program would have automated recognition and delineation. Human experts appear to be better than the computer at recognition whereas the computer is better and faster at delineation.

Problems that must be solved for computerized lesion quantification include the following. (i) Lesions in multiple sclerosis and images, in general, are inherently fuzzy with 'soft' rather than 'hard' boundaries. (ii) There is significant variation in the conspicuity of lesions. (iii) Multiple sclerosis lesions may be small in size and large in numbers. (iv) There are many artifacts from the scanner, patient motion, and other sources such as blood and CSF flow. (v) It is difficult to determine the true accuracy of any method; there is no ideal 'gold standard'.

There are many methods that have been implemented in the attempt to quantify lesion burden. In the manual tracing approach the trained operator outlines the lesion. Results obtained using this approach have shown that intra-observer variability can be as low as 6% in experienced hands, but that inter-observer variability can be as high as 14–20% for (Paty *et al*., 1993, 1994; Gonzales *et al*., 1994). Threshold-based lesion methods require different degrees of operator assistance and improve variability for volume determinations compared with manual tracing (Pannizzo *et al*., 1992; Wicks *et al*., 1992; Grimaud *et al*., 1996). However, in case of false negatives (missed lesions), false positives or wrongly delineated lesions, these techniques either ignore them or require considerable operator assistance. Additionally, small

threshold changes can result in very significant changes in lesion load (Filippi *et al*., 1996*d*). Local (lesion-by-lesion) thresholding techniques use the advantage of expert recognition and computer delineation; they take about as long as manual outlining to perform, but with substantially better precision (Grimaud *et al*., 1996). Feature space partitioning (clustering) is based on the classification of brain tissue and its intensity behaviour on a variety of pulse sequences; brain, CSF and lesion can then be identified and quantified. There is technique variability depending upon the exact clustering strategy and methodology with one report providing intra- and inter-observer variability of 4.4 and 10.6%, respectively (Simon *et al*., 1997). Another approach is based upon fuzzy topological principles with white matter, grey matter, CSF and lesions depicted as fuzzily connected 3D objects. The inter- and intra-observer coefficient of variation is ~1% with 5–40 min of computational time (SPARC 10 with 64 MB RAM) and 1–15 min of expert time per 2D multi-slice brain study (Udupa *et al*., 1997).

2. The role of MR in diagnosis

Before discussing the relationship of specific MRI criteria to the diagnosis of multiple sclerosis, there are two aspects relating to the use of MRI criteria in the diagnosis of multiple sclerosis that deserve special attention. First, the diagnosis of multiple sclerosis is based fundamentally on clinical evidence (Poser *et al*., 1983), and MRI findings should only be considered as support for the clinical diagnosis; it follows that when clinical evidence of multiple sclerosis is absent, MRI abnormalities alone are not sufficient for a diagnosis. Secondly, it is important to note that various MRI criteria differ with respect to sensitivity and specificity in assisting in the diagnosis of multiple sclerosis. Some parameters, such as the number of lesions, are sensitive but have low specificity. In contrast, other parameters such as the location of lesions are more specific but have lower sensitivity. Despite these caveats, MRI is a very useful paraclinical tool for supporting and making more certain the diagnosis (the demonstration of disseminated lesions in space can upgrade the diagnosis from clinically probable to clinically definite multiple sclerosis using the Poser criteria), and for exclusion of other conditions.

In 1988, two research groups published sets of recommendations relating to the use and interpretation of MRI findings in the diagnosis of multiple sclerosis (Fazekas *et al*., 1988; Paty *et al*., 1988; see Table 1). These recommendations focus mainly on number of lesions and are based solely on conventional PD/T_2-weighted brain images.

In the cerebrum, lesions in the periventricular region are considered to increase the likelihood of the diagnosis of multiple sclerosis. Many diseases other than multiple sclerosis can also produce areas of increased signal in the centrum semiovale and areas of increased signal can occur as part of the aging process, but these lesions tend not to be in the periventricular region. Lesions in the temporal horn may also be relatively specific for multiple sclerosis but have low sensitivity since their frequency is low. With respect to the importance of lesion location some difference of opinion is found with respect to the importance or interpretation of lesions close to the cortical mantle since lesions in these areas can be associated with other processes such as systemic lupus erythematosus. However, recent studies have shown that one of the MRI criteria that has the highest specificity (for patients with monosymptomatic neurological disease to progress to multiple sclerosis) is juxtacortical lesions (Barkhof *et al*., 1997). Lesions in the brainstem are also more common in multiple sclerosis that with other illnesses. Focal lesions within the corpus callosum are also relatively common in multiple sclerosis, and the appearance of a moth-eaten change or atrophy is relatively specific for multiple sclerosis. Finally, involvement of the spinal cord can be extremely helpful in assisting the diagnosis of multiple sclerosis; a high proportion of patients with suspected multiple sclerosis but without lesions in the cerebrum will have lesions in the spinal cord (Thorpe *et al*., 1996*a*).

Table 1 *MRI findings strongly suggestive of multiple sclerosis**

Paty (1)	Four lesions of $\geqslant$3 mm
Paty (2)	Three lesions, one of which is periventricular
Fazekas	Three or more lesions with at least two of the following characteristics (a) >5 mm (b) periventricular (c) infratentorial

*From Paty *et al*. (1988) and Fazekas *et al*. (1988).

Some controversy exists with respect to the importance of enhancing lesions as an aid in the diagnosis of multiple sclerosis. Recent evidence indicates that while contrast-enhancing lesions have low sensitivity, since they are found, overall, in probably less than half of patients undergoing diagnostic evaluations, the presence of enhancing lesions are more specific for multiple sclerosis when compared with vascular disease, especially if multiple lesions are seen (on the other hand multiple enhancing lesions can be seen in granulomatous and metastatic disease). The recent study examining the MRI parameters that are most predictive of patients with monosymptomatic disease progressing to multiple sclerosis found that, in addition to the juxtacortical location, contrast enhancement has the highest predictive value (Barkhof *et al*., 1997); a finding that indicates that sequences sensitive to changes in tissue T_1 should be part of the diagnostic evaluation of patients.

Some evidence suggests that fast-FLAIR sequences result in better definition of areas of increased signal than PD/T_2-weighted CSE or FSE images. Adequate longitudinal comparison of results obtained with FLAIR and CSE or FSE are still lacking. Similarly, the number of enhancing lesions seen following administration of gadolinium chelate are

greater using MT sequences or by the administration of a triple dose of contrast agent as compared with the use of single dose of gadolinium DTPA on standard T_1 sequences. As with the comparison of fast FLAIR with CSE or FSE, the results obtained with MT post-contrast or triple-dose images are not well understood and little natural history data exists. Consequently, at present, PD/T_2-weighted FSE or CSE (always) and T_1-weighted single-dose post-contrast images (sometimes) should be the standard imaging protocols used in diagnostic tests.

3. Natural history studies in understanding the disease multiple sclerosis

Conventional T_2-weighted images

Early studies imaging post-mortem material demonstrated a good correlation between areas of diseased tissue and areas of increased signal on T_2-weighted images (Stewart *et al*., 1984; Ormerod *et al*., 1987). Studies of the natural history of multiple sclerosis using T_2-weighted images provided a new understanding of the disease process. New clinically silent areas of increased signal were often observed; it was shown that they occurred ~5–10 times more frequently than clinical disease in patients still in the relapsing phase of the disease (Isaacs *et al*., 1988; Willoughby *et al*., 1989).

The total load of disease can be evaluated using a variety of techniques that have been discussed previously. Based on results obtained from yearly follow-up of patients in the placebo arm of the phase III trial of interferon beta-1b, patients with relapsing–remitting multiple sclerosis show a yearly increase in burden of disease as seen on T_2-weighted images of between 5 and 10% (IFNB Multiple Sclerosis Study Group, 1995). These results have shown that multiple sclerosis is progressive during the relapsing–remitting phase of the disease. With more frequent assessment of T_2-weighted lesion load, substantial variation has been observed. This variation is considerably greater than can be explained by measurement errors and, as will be examined later in this review, the biological variation has important implications for the use of MRI in monitoring experimental therapies.

Contrast-enhanced lesions

Some initial studies of contrast-enhancing lesions indicated that most new lesions seen on monthly T_2-weighted images begin with disruption of the BBB in relapsing–remitting and secondary progressive disease (Miller *et al*., 1988*b*; Bastianello *et al*., 1990; Harris *et al*., 1991; Thompson *et al*., 1991, 1992; Barkhof *et al*., 1992). The concept that BBB leakage is a consistent early feature of lesion evolution has been strengthened by recent studies which have imaged patients at weekly intervals and found that all new lesions seen on T_2 are initially observed as areas of BBB disruption (Lai *et al*., 1996). Also, a few enhancing lesions appear without an accompanying T_2 lesion, and a few older lesions show re-enhancement (Miller *et al*., 1993). Over 75% of enhancing lesions show BBB disruption for $\leqslant$1 month (Smith *et al*., 1993). Approximately 20% continue to enhance for $>$1 month and a smaller number (5%) persist for 3–4 months. Lesions demonstrating enhancement for $>$4 months should be re-evaluated for their relationship to multiple sclerosis; such an appearance is more suggestive of other inflammatory, infectious or neoplastic diseases.

Studies of the natural history of multiple sclerosis using contrast-enhanced images have taken two approaches: (i) longitudinal or serial studies of small cohorts of patients and (ii) cross-sectional studies of larger cohorts. A recently completed analysis of 100 patients with relapsing–remitting multiple sclerosis and mild disability indicate that when patients are imaged for three serial months, ~72% of them have evidence of BBB disruption on at least one of the months (H. McFarland and J. Franks, workshop presentation). The mean enhancing lesion frequency over the 3-month period was 4.6. Since the cohort included some patients with very high lesion activity (24, 36 and 64 lesions per month) the median value of 1.6 for lesion activity probably provided a better estimate of lesion activity in this cohort. These findings indicate that in this population of early relapsing–remitting multiple sclerosis patients, disease activity, as measured by contrast-enhanced MRI, is generally high and confirms the previous conclusions based on T_2 activity in clinically stable patients, and that the disease is active and progressive in a substantial number of patients even early in the disease course. Studies of the 100-patient cohort indicate that a previously identified association in 68 patients between increased lesion activity and gender (higher in males) (Stone *et al*., 1995) is not confirmed in the larger cohort. This change indicates the need for studies of large populations to provide an accurate estimate of lesion frequency in the overall multiple sclerosis population. However, the previously observed association of increased lesion activity in patients with onset of disease prior to the age of 20 years was confirmed as was the association of increased lesion activity in patients with EDSS scores of $\geqslant$4 compared with those with milder disability (Stone *et al*., 1995).

Longitudinal studies of patients have confirmed the active nature of the process in patients with mild clinical multiple sclerosis and have also demonstrated fairly marked month-to-month biological variation. Several studies have now reported serial contrast-enhancing MRI data from patients with relapsing–remitting multiple sclerosis followed from several months to $>$5 years (Smith *et al*., 1993; Thorpe *et al*., 1996*b*). Although the number of enhancing lesions fluctuates considerably from month to month, each patient tends to remain in a particular range of lesion activity. For example, a patient with an average lesion frequency of one lesion per month tends to show a similar lesion frequency over several years (McFarland *et al*., 1992). When the lesion activity is assessed over time, in 6 months blocks, no significant increase or decrease in lesion activity has been noted over a 2-year period. Thus, regression to the mean does not appear to occur

within this study window. However, it is important to note that as the number of months used to estimate a patients lesion frequency decreases, the likelihood of under- or over-estimating the true lesion frequency for that patient increases; estimates based on assessment of <3 months probably has little validity for an individual patient.

Just as with T_2 lesions, a majority of enhancing lesions occur in clinically stable individuals. However, a significant association between the occurrence of enhancing lesions and exacerbations has been found in longitudinal studies, and has been confirmed in several cohorts. Thus, periods of increased lesion activity appear to increase the risk of exacerbation probably by increasing the risk of lesions occurring in areas of the CNS that will become clinically apparent.

Natural history of MRS studies

In addition to standard imaging sequences, the examination of metabolites from the tissue may provide valuable information not available on images. In particular, the study of changes in *N*-acetyl apsartate informs us about axonal status (Arnold *et al*., 1990; Davie *et al*., 1995), and detection of abnormal lipid peaks may indicate myelin disruption (Wolinsky *et al*., 1990). The technique can be applied in various ways for examining changes occurring over time. Distinct from the use of single-voxel studies examining the spectra from a particular region-of-interest, whole-slice studies can be performed. In one of the most extensive studies, a slice of $8 \times 8 \times 1.5$ cm located immediately above the lateral ventricles was studied (J. Wolinsky, workshop presentation). The spectra were analysed in 0.8 cm^3 voxels. Twenty-five patients with clinically definite multiple sclerosis but with mild to moderate disability were studied in a serial manner for a total of 126 examinations over 4–10 months. Following the MRS examination, pre- and post-contrast T_1-weighted images were obtained. In general, the metabolic maps of choline-containing compounds, creatine/phosphocreatine, NAA, inositol and lipid were similar in normal control subjects and patients. However, in regions of lesions, the NAA was found to be inversely correlated with the T_2 lesion volume ($r = -0.54$). Thus, as the volume of the lesion increases, the NAA decreases, suggesting that in lesions in these patients with relatively mild multiple sclerosis, decreases in NAA are seen suggesting possible early axonal damage or dysfunction. Further, in 11 of the 126 examinations, increases in the region thought to represent lipid were observed. This increase was seen in some but not all acute lesions as identified by enhancement. In four instances lipids were observed in normal-appearing white matter, raising the possibility of changes that occur independent of lesion parameters usually associated with multiple sclerosis and that alterations in myelin could precede immunological mechanisms in some instances. Clearly, observations such as these will require careful validation and must be interpreted conservatively with appreciation of the technical pitfalls in the methodology, such as regional variation in the metabolite concentrations, motion, and both single voxel and chemical shift imaging artifacts. Nevertheless, the use of MRS may now begin to provide some valuable insights into lesion evolution.

Clinical correlations of MR in established multiple sclerosis

The relatively modest correlations between disability and conventional MRI parameters, in particular T_2 lesion load, have been disappointing, raising the possibility that MRI may provide a poor reflection of the processes in multiple sclerosis that are most closely linked to disability. However, in viewing this problem, one must consider a number of issues. First, multiple sclerosis is a disease with considerable clinical complexity. It has been pointed out that any specific aspect of disability such a decreased mobility can have many different components such as corticospinal tract involvement, posterior column damage, decreased vision, etc. Secondly, even relapses which are generally considered easy to identify can be highly variable and difficult to quantify. Thirdly, the scales used to measure the levels of involvement in multiple sclerosis are complex and the most commonly used, the EDSS, measures both impairment and disability at different regions of the scale (Kurtzke, 1983; Rudick *et al*., 1996); furthermore, this scale is non-linear and may often be used to monitor disability incorrectly. Fourthly, correlations are often made with what is thought to be irreversible deficit but this can be due to either irreversible recovery from an acute exacerbation or slow progression, which produce similar clinical changes but may have different mechanisms and might be expected to show correlations with different MRI parameters. Finally, problems with measurement error in quantifying MRI parameters, especially lesion load, could reduce the ability to obtain correlates, although perhaps even more important is the evidence from existing data that the biological variation of some MRI parameters is much greater than measurement error. For example, substantial month to month fluctuations in T_2 lesion load have been identified, and they could introduce error into studies attempting to establish relationships between single measures of lesion load and clinical disease in a cross-sectional manner in a small cohort of patients. Clearly, longitudinal and prospective studies are needed to overcome this high degree of variance in measures of either lesion load or the occurrence of new lesions.

When specific correlations between various MRI parameters and measures of clinical disease are examined, reasonably good correlations are found between exacerbations and enhancing lesions. As has been mentioned previously, enhancing lesions are seen between five and 10 times more often than clinical relapses but the latter occur more often during periods of increased BBB disruption detected on MRI (Thompson *et al*., 1991; Smith *et al*., 1993). In some cases, specific associations between lesions and clinical presentation

can be observed and this has best been demonstrated in optic neuritis (Youl *et al*., 1991). Since most of the enhancing lesions seen are in the cerebrum, the correlation between MRI activity and clinical disease might increase if cognitive dysfunction was studied (discussed later).

Notwithstanding all of these observations, the relationship between T_2 lesion load and disability in established multiple sclerosis is disappointingly weak; typical correlations (ρ-values) have been in the range of 0.15 to 0.46 (Gass *et al*., 1994; Filippi *et al*., 1995*b*; Gasperini *et al*., 1996). In the large relapsing–remitting multiple sclerosis cohort studied in the interferon beta-1b study, a correlation of only 0.23 was observed (IFNB Multiple Sclerosis Study Group, 1995).

While these weak correlations are no doubt influenced by the issues discussed above, the low pathological specificity of T_2-weighted abnormalities—in particular the inability to distinguish pathological characteristics of the lesion which may represent the greatest contribution to dysfunction, namely demyelination and axonal damage—is likely to contribute in an important way. The use of new imaging techniques thought to be more specific for these pathological features may eventually provide stronger correlations. For example, in primary progressive multiple sclerosis the most significant correlation has been found with diameter of the spinal cord at C2 (Losseff *et al*., 1996*a*). The diminished cord diameter may reflect the importance of axonal damage in this form of the disease. Progressive cerebral atrophy has also been reported to correlate with increasing disability in a cohort of patients with relapsing–remitting and secondary progressive multiple sclerosis (Losseff *et al*., 1996*b*). Several other putative markers of demyelination and/or axonal degeneration (e.g. hypointense T_1 lesion load, low magnetization transfer ratios and reduced NAA) have also been correlated more strongly with disability.

Cognitive changes in multiple sclerosis

Since a large number of lesions in the cerebrum seem to occur without detection on the neurological examination, it seems likely that some alteration in cognitive function could accompany these changes. Cognitive dysfunction is indeed common; it is characterized as defects in attention, visual spatial and short-term memory, and in executive function, and is found in ~50% of patients. The relationship between cognitive function and MRI parameters of disease can be examined using three different approaches; the overall relationship, the relationship between lesion location and specific cognitive changes and the relationship between MRI and cognitive changes occurring in longitudinal studies. With respect to the overall relationship, correlations between cognitive test performance and several MRI measures such as total lesion load, ventricular size and size of the corpus callosum have been reported. When the amount of shared variance is examined between psychological test scores, lesion burden on MRI and clinical measures of disability, the shared variance between test scores and burden of disease was found to be 36% while that between scores and clinical measures of disability was only 3% (S. Rao, workshop presentation). Thus, reasonable correlations are generally found between extent of disease seen on MRI and cognitive function.

Considerable effort has been focused on identifying relationships between the location of multiple sclerosis lesions and cognitive dysfunction and these studies fall into two general areas of examination; disconnection syndromes and the effect of frontal lobe lesions. Since involvement of white matter in the cerebrum is common and often extensive, even in patients early in the course of multiple sclerosis, disconnection syndromes would be expected to be common. In fact, reports of specific disconnection syndromes such as conduction aphasia have been relatively uncommon. However, studies testing interhemispheric communication using a dichotic listening paradigm have indicated defects (Jacobson *et al*., 1983; Rubens *et al*., 1985). The results of these studies indicate that verbal information processed by the right hemisphere does not effectively cross the corpus callosum for processing in the language areas of the left hemisphere. The defect in interhemispheric communication was related to atrophy of the corpus callosum as seen on MRI (Rao *et al*., 1989).

Several correlations between the location of multiple sclerosis lesions and cognitive abnormalities have been reported. One study demonstrated a relationship between lesions in the left frontal lobe and perseverative responses on the Wisconsin Card Sorting Test, suggesting a relationship between the location of lesions in the frontal lobe and conceptual reasoning (Swirsky-Sacchetti *et al*., 1992). However, the specificity of these observations has been questioned since a correlation was also found with total lesion burden. A recent study has re-examined this issue by first subdividing patients into those with lesion burden of $\geqslant$20 cm and those with a lower lesion burden. The former group was subdivided into those with and those without frontal lesions. Both groups with high lesion burden scored poorly for verbal IQ, but the group with frontal lesions had a significant increase in perseveration on the Wisconsin Card Sorting Test providing additional support for a relationship between lesions in the frontal lobes and conceptual reasoning (Arnett *et al*., 1994).

In short-term serial studies conflicting results have been reported; both an increase and a lack of change in cognitive impairment in relationship to increase in lesion load has been described. The differences in these studies may be due to the short period of follow-up and differences in patient selection. In a 4–5 year follow-up study of patients initially presenting with monosymptomatic disease, an increased impairment in attention was reported in patients progressing to clinically definite multiple sclerosis and with increased lesion burden on MRI (Feinstein *et al*., 1992). A second study, which is currently ongoing, has evaluated change in cognitive function in 77 patients over a 3-year period (S. Rao, workshop presentation). Of these, 15 patients have had

a decrease in cognitive function; this cohort also had an increase in lesion burden of 15 cm^3 compared with a mean of 5 cm^3 in the patients without increasing cognitive dysfunction. The group with worsening cognitive function had a slightly greater increase in EDSS, but the difference compared with the cognitively stable cohort was not significant.

Overall, a general correlation between cerebral lesion burden and change in cognitive function can be identified, but the relationship is not well understood. Certainly, the location of the lesions as well as the overall lesion load has a substantial effect on cognitive function and additional longitudinal studies will be needed to resolve these relationships. Greater attention also needs to be given to correlations with imaging parameters other than lesion load on T_2-weighted images. Correlations with hypointense lesions and enhancing lesions as well as regional changes in MTR may be particularly important (van Buchem *et al*., 1996*b*).

Prognostic utility of MRI in clinically isolated syndromes

The value of MRI changes in predicting which patients presenting with monosymptomatic disease will go on to develop clinically definite multiple sclerosis has considerable importance both from the stand point of selecting patients for clinical trials focusing on the early stage of the disease (an approach advocated by a recent position paper) and on the routine management of patients as new treatments evolve that may have their greatest effectiveness when used early in the course of the disease. The issues relating to the prognostic value of MRI relate back to many of the issues discussed previously in regard to the use of MRI parameters for the diagnostic evaluation of patients. First, the diagnostic specificity and sensitivity of a particular MRI parameter is of particular importance. Secondly, the natural history of all MRI parameters is closely linked to understanding the prognostic value of MRI. Both areas have been discussed in some detail. Several studies have examined the ability of the magnitude of various MRI alterations found at the time of presentation with monosymptomatic disease to predict the evolution to definite multiple sclerosis or to increased disability. Studies focusing on the number of lesions at the time of presentation have found that abnormal images defined as four or more T_2 lesions have a positive predictive value of 65% of developing clinically definite multiple sclerosis within 5 years (Morrissey *et al*., 1993). Similarly, a study of patients presented with optic neuritis found that patients meeting the Paty criteria grade IV (four lesions or three lesions with one periventricular) had a 35% likelihood of developing definite multiple sclerosis in 2 years (Beck *et al*., 1993). A study looking at lesion load rather than number (using a global thresholding technique) and arbitrarily dividing those with abnormalities into high and low lesion load groups, has reported a positive predictive value of 90% for developing multiple sclerosis in those with a high lesion load at presentation (Filippi *et al*., 1994). Importantly, a negative predictive value of 6% was reported for patients with normal MRIs at the time of presentation. In a recent study a higher positive predictive value was found when the presence of contrast-enhancing lesions and location of the lesions in the juxtacortical region were both incorporated into the criteria (Barkhof *et al*., 1997). A recent 10-year follow-up study has provided further information on the risk for long-term disability; those with $\geqslant$10 lesions at presentation were most likely to have an EDSS of $>$3 (O'Riordan *et al*., 1996*b*).

Overall, the predictive value of MRI seems sufficient for the selection of patients for clinical trials, targeting the prevention of progression to definite multiple sclerosis as an outcome measure. Further, the predictive value of abnormal MRIs at the time of presentation is sufficient for consideration of new treatments which may be especially effective early in the disease course. As with any treatment the potential risks of the treatment need to be balanced against the benefits which, in this case, would include the treatment of a proportion of patients who might not develop multiple sclerosis or who would not, if untreated, develop significant disability over a reasonable period of follow-up. Larger prospective studies incorporating various MRI parameters would be needed to define the predictive role of MRI in more detail. However, it will become more difficult to perform such natural history studies because of the increased use of approved disease modifying treatments.

MRI and immune system markers

Since multiple sclerosis is thought to have an immunopathological basis, and since MRI is thought to provide a highly sensitive measure of disease activity, it is reasonable to suppose that immunological changes could be found that would correlate with disease activity on MRI. Unfortunately, most studies that have looked at this question have found correlations that are relatively weak. These have included soluble levels of adhesion molecules (Hartung *et al*., 1995; Giovannoni *et al*., 1996; Calabresi *et al*., 1997).

A recent study has evaluated the phenotypic profile of a cohort of patients including both relapsing–remitting and secondary progressive. The results indicate that a correlation can be found between the number of gadolinium enhancing lesions and a decrease in the percentage of CD29+ T cells (H. Weiner, workshop presentation) although a similar relationship was not identified in a smaller serial MRI study (Stuber *et al*., 1996). Also a decrease in the percentage of CD4+CD26+ T cells and an increase in the lesion load has been observed.

The overall failure to identify strong associations could raise doubts regarding the immunological events underlying the disease. More likely, examination of phenotypic profiles of immunological parameters in the peripheral blood lack sensitivity to detect changes that might be expected to

occur. However, it remains clear that correlations between immunological markers and disease activity need to continue to incorporate MRI measures of disease activity since clinical measures reflect only a small portion of ongoing disease.

4. MR application in clinical trials

Background

MRI has become established as a very important tool in monitoring the efficacy of new therapies in multiple sclerosis. Virtually all new clinical trials have an MR component for therapeutic monitoring. MRI is obviously attractive in this regard as it provides objective and direct evidence of the evolving pathological process and its modification by treatment. It also provides a rapid and sensitive measure of treatment outcome in early relapsing–remitting and secondary progressive disease. However, there is much controversy regarding its definitive role, largely because the correlations between MRI and clinical status are generally modest.

Guidelines of the US Multiple Sclerosis Society's task force for monitoring treatment

In early 1996, a task force of the US Multiple Sclerosis Society published guidelines for the use of MR techniques in monitoring treatment (Miller *et al*., 1996). The task force consisted of neurologists and neuroradiologists with extensive experience in the application of MR in multiple sclerosis, as well as a statistician. There were three main recommendations of this task force. First, because of the high sensitivity of serial monthly T_2-weighted and gadolinium-enhanced brain MRI in detecting asymptomatic disease in early relapsing–remitting and secondary progressive multiple sclerosis ($\geqslant$10 new enhancing lesions for every clinical relapse), MRI activity outcomes based on these sequences are recommended as the primary measure of treatment efficacy in exploratory studies of new agents in these clinical subgroups. There is quite a good correlation between the presence and number of gadolinium enhancing lesions and the occurrence of clinical relapse (Grossman *et al*., 1986), and short-term fluctuations in EDSS as a result of relapse.

The second major recommendation was that MRI should be only a secondary outcome measure in definitive (phase III) trials in early relapsing–remitting and secondary progressive multiple sclerosis. This is because T_2-weighted and gadolinium-enhanced abnormalities correlate only modestly, if at all, with long-term progression and disability measured using the EDSS. Thirdly, it was noted that the number and extent of MRI abnormalities at presentation with a clinically isolated syndrome suggestive of multiple sclerosis (e.g. isolated optic neuritis) is strongly predictive of the risk of conversion to clinically definite disease over the next 1–5 years. Therefore, it was recommended that MRI is used to define appropriate cohorts for entry into trials aimed at preventing conversion from an isolated syndrome to definite multiple sclerosis.

The task force also noted that exploratory studies, if negative, could be used to avoid going onto the burden of a large phase III trial, providing it was thought that the mechanism of the drug effect should be seen through suppression of gadolinium enhancement (indicating BBB-impairment and probably inflammation). However, if the trial was positive, there would still be the need for a phase III trial, since the predictive value of short-term MRI for long-term disability is uncertain, and there would be a need to evaluate persistence of effect, as well as safety aspects in a larger cohort.

Looking to the future, the task force emphasized the importance of more rapid and accurate quantification of MRI abnormalities, and the need to improve the correlations with clinical course, especially progression towards irreversible disability. In the last respect, new putative markers of demyelination and axonal loss, the pathological substrates of disability, were seen as particularly important.

Quality control

Quality control issues have become of major importance, particularly with the application of quantitative methods of analysis to electronic data, and the multicentre nature and length of orthodox phase III clinical trials. In a typical study lasting several years, the scanner may alter its performance, especially if there have been upgrades or repairs. Sometimes it is necessary even to change scanners during a study. A parallel groups trial design with a control arm may still allow treatment effect to be observed, even if change in machine performance leads to a step change in accuracy for all participants. The latter however, decreases confidence in the results, and loses the chance of obtaining valuable natural history data. It may also reduce the power of the study. To avoid step changes, measurements should relate to the state of the subject at the time of scanning, and be independent of the scanner, as far as possible.

The nature and frequency of quality assurance procedures will depend on the nature and frequency of scan sequences, and will also be influenced by scanner changes. Quality assurance data should be obtained before and after major upgrades, equipment repairs, or changes in personnel (e.g. a new technician/radiographer). A quality assurance scanning budget of perhaps 10–20% of patients scanning time and cost should probably be allocated. Phantoms are useful for quality assurance serial scanning. Their physical parameters can be accurately determined, but there may be a problem with their stability over time, and they may not represent the biological state of tissues. Further work is particularly needed to develop a stable phantom for measuring MTR. Usually a mixture of phantoms and human control subjects is optimal. In serial 2D imaging, close attention to repositioning is important to improve precision in measuring real changes in lesion load and activity. Voxel size can be monitored by

imaging a regular geometric phantom of known dimensions. This can be important when measuring total lesion volumes or progression in atrophy, as a change in voxel size will affect the biological outcome measured. Uniformity correction can also be important, particularly when measuring lesion volume with fully automated techniques.

Statistical issues in MR-supported trials

Several statistical issues exist, and these include the choices of response variables, methods of analysis, and trial design, as well as sample size calculations and designs for interim analysis. Means and standard deviations are critical in comparing continuous variables such as T_2 lesion load, or count variables such as the number of gadolinium enhancing lesions. The sample sizes required to show a given treatment effect when compared with placebo (or untreated) control subjects will depend upon the amount of the MR activity measured over time as well as the variability of the data amongst both the control subjects and the treated patients. If a group of treated patients is used as the control arm, and if the treatment alters the overall amount of the MRI activity and its variability, very different sample sizes will be required. Sample sizes also depend on the method of analysis that will be used. The Wilcoxon rank sum test can be applied for comparing two groups on a continuous variable (e.g. lesion load), counts (e.g. numbers of lesions) or ordinal data (e.g. EDSS).

In multiple sclerosis, the impact of measurement error may be relatively unimportant, if it is much less than the biological spread of the activity measures, i.e. the biological variability will be the dominant factor in determining sample size. Based on an evaluation of the T_2 lesion loads obtained by manual outlining and a semi-automated contour technique applied to single scans on several occasions (Grimaud *et al*., 1996), Petkau has calculated that manual outlining errors would lead to only a 2% increase in sample size and contouring to a 0.2% increase. However, these calculations are based on the reproducibility of measurements from single scans. In a treatment trial, it is more important to look at the reproducibility of change in MRI lesion load over time. Such analyses have yet to be undertaken.

Using data from the interferon beta-1b North American relapsing–remitting trial, Petkau (1996) has simulated measurement error by introducing noise to increase the variability of the results artificially. He found that with noise variability as high as 40%, there was still a statistically significant difference in lesion load accumulation between the placebo group and those receiving 8 MU of interferon beta-1b on alternate days ($P = 0.04$). This indicates that the methodology used in this trial for measuring lesion load (manual outlining) was easily able to demonstrate the treatment effect and probably would have done so in a substantially smaller cohort than was studied in this trial.

Other statistical issues include how to handle the situation when multiple raters analyse MRI outcomes. With the large numbers of scans used to measure T_2 lesion load in definitive trials, several raters may be needed to complete the task if manual outlining or semiautomated local thresholding techniques are employed. This is probably acceptable if the same rater reports each serial scan for individual patients, although it may be necessary to do post-stratification analysis for different raters. Interim analysis is also a complex issue (Petkau, 1996), particularly in the typical situation with MR responses where data on individual patients is being accumulated over time. If MRI is the primary outcome measure, and an interim analysis is planned which might form the basis of stopping the trial if efficacy has been established, strategies are needed which control the overall Type I error (for a more detailed discussion, see Petkau, 1996). If one analyses treatment effect at each time point separately, there will be a greater risk of obtaining spurious results, although there are statistical methodologies which provide substantial gains by making slightly more detailed use of longitudinal data than is typically done (Frison and Pocock, 1992).

Specific therapeutic trial designs

Background

In considering trial designs three general points should considered. First, the MRI design should be tailored according to the proposed mechanism of action of the drug. Secondly, most trials currently use conventional T_2-weighting and gadolinium enhancement, so there is a particular need to incorporate new putative markers of demyelination and axonal loss and to evaluate their sensitivity to change, reproducibility and ability to show treatment effects over time. Thirdly, the designs currently suggested will undoubtedly change as new information becomes available.

Optimal MR design in pilot therapeutic trials

These trials are essentially confined to relapsing–remitting and secondary progressive multiple sclerosis, as there is much less MRI activity in the primary progressive group. Monthly brain scanning with T_2-weighted and gadolinium-enhanced imaging (0.1 mmol/kg of gadolinium chelate) is employed in these studies. A parallel groups design with a placebo arm required about 2×40 patients to show a 60% reduction in new enhancing lesions over 6 months (McFarland *et al*., 1992). A 1-month run-in scan reduces the required sample sizes by ~30% (Nauta *et al*., 1994). Somewhat larger sample sizes are probably required in secondary progressive multiple sclerosis (Tubridy *et al*., 1997). Crossover designs are more powerful, because there is less intra-patient than inter-patient variability in MRI activity. A single crossover design with 6 months run in (untreated) followed by 6 months of treatment requires 10–12 patients to show a 60% reduction in activity. Double crossover designs are equally powerful, but there needs to be a wash out period between the two

phases, probably a minimum of 2–3 months, and potentially longer for some therapies. Single crossover designs may also be contaminated by regression to the mean, and probably at least 6 months of treatment observation is desirable. A 3-month period may be complicated by a delay in treatment onset. If a safe, cheap drug shows a 50–60% reduction in a small crossover study, this could justify going straight to a phase III trial. If the drug has more side effects or expense, a parallel group design with the larger sample sizes (e.g. 2×40 for 6 months) should be performed to gain more certainty about the MRI effect.

In pilot studies, sample size may be reduced by selecting only those with enhancing lesions during run in; about two thirds of relapsing–remitting or secondary progressive patients will show one or more enhancing lesions over a 3-month period. Selection of these patients may, however, lead to a biased subgroup, more likely to respond to treatment, and it is uncertain how to extrapolate the results to the general group for phase III clinical outcome studies.

MRI has some potential to look at responsiveness at an individual level. The work with interferon beta-1b at the National Institutes of Health, Bethesda, USA, points to heterogeneity of treatment response (H. McFarland, workshop presentation). Of 32 patients treated, the majority have shown a complete cessation of new enhancing lesions, at least over the first 6 months. Seven patients were classified as non-responders, in that they failed to show a 60% reduction in the number of enhancing lesions. There were rather more non-responders in the group developing antibodies to interferon beta-1b.

There is a need to evaluate serial fast FLAIR in exploratory trials as potentially, it will increase the detection of new lesions, though how much it will do so over and above T_2-weighted and gadolinium-enhanced scanning is unclear. Preliminary experience with triple-dose gadolinium reveals a 50% increase in new enhancing lesions (Filippi *et al*., 1997*b*), and this approach combined with delayed scanning and magnetization transfer, which together more than double the overall yield of all enhancing lesions (Silver *et al*., 1997*a*), should be an important way of increasing sensitivity in the future. In pilot studies other markers such as T_1 hypointense lesions, spinal cord imaging, and magnetization transfer imaging are not yet validated as useful tools, but need to be studied.

Optimal MR design in definitive trials

MRI should be considered mandatory for two reasons. First, it provides additional information concerning treatment effect, over and above the primary clinical outcomes (usually disability or relapse rate). Secondly, there is an opportunity to learn about the disease and the MR measures themselves. The application of multiple MR parameters in large clinical trials at this time will provide a unique opportunity to validate them with respect to the evolving clinical course. While it may not be mandatory for patients to have brain MRI abnormalities to enter a trial, such abnormalities will probably be necessary if there are atypical clinical features, e.g. a primary progressive course. The presence of spinal MRI lesions may also be included in the selection criterion, especially in the primary progressive group in whom there is often a paucity of brain lesions. T_2-weighted brain imaging to measure total lesion load is the simplest sequence to acquire, and should be obtained in all cases to allow measurement of total lesion load. As a minimum, an entry and exit scan should be obtained. More frequent scanning may be advantageous, e.g. to increase the sensitivity of the experiment, and to compensate for short-term (month to month) fluctuations, two run in and two exit scans close together will be useful. More frequent scanning during the trial allows an assessment of changes in efficacy over the course of the trial, e.g. with the development of drug antibodies. T_2-weighted scans can also be used to count the number of new or enlarging lesions.

Concerning other MR parameters, gadolinium enhancement is useful (Jacobs *et al*., 1996), but is probably only needed in a subgroup and at some but not all centres. Enhanced scanning on a monthly or less frequent basis throughout several years of the study will help to assess changes in treatment effect over time. Perhaps of greatest importance is to include in current phase III trials as many of the putative markers of demyelination and axonal loss as possible. These include MT imaging, T_1 imaging for hypointense lesions, proton MR spectroscopy, diffusion imaging, quantification of atrophy and T_2 magnetization decay curve analysis. Preliminary studies have revealed strong correlations with disability, cross sectionally and longitudinally, for a number of these parameters. There are complex issues with respect to their implementation in multicentre trials, including standardization of acquisition across centres, reproducibility and stability of the measurements and sensitivity to change over time. These issues should be addressed because of the potential importance of the techniques for prognosis with respect to long-term disability. In measuring outcomes at the end of a trial, one may wish to perform subgroup analyses, stratifying patients, e.g. according to T_2 lesion load or the presence of enhancing lesions at baseline.

Optimal design in clinically isolated syndrome trials

It is appropriate to consider the site of the syndrome (e.g. optic neuritis, partial myelitis), the rate of onset (e.g. acute myelopathy versus chronic progressive spastic paraparesis), and the age of the patient in both clinical and MRI work up. MRI abnormalities at presentation with an acute syndrome predict a $>80\%$ chance of relapses leading to a diagnosis of multiple sclerosis in the next 10 years (O'Riordan *et al*., 1996*b*). This prognostic data is confined to those under 50 years of age; cerebral white matter abnormalities are much

less specific in older patients, and onset with acute episodes is also unusual over the age of 50 years.

There are diagnostic issues of relevance in this group. The distinction of multiple sclerosis from acute disseminated encephalomyelitis is important. More work is needed with a range of new MR parameters more specific for demyelination and axonal loss, to see if these might distinguish multiple sclerosis from acute disseminated encephalomyelitis. The predictive value of these new parameters for the future clinical course is also important, as is the sensitivity of conventional and non-conventional MR parameters over time as possible secondary outcome measures in trials aimed at preventing conversion from an isolated syndrome to definite multiple sclerosis. The sensitivity and value of serial monthly gadolinium-enhanced MRI in such patients is completely unknown.

Application of MR techniques to other clinical trial settings

New clinical trial scenarios which have had little attention to date are primary progressive multiple sclerosis trials, the treatment of acute relapses, and treatments aimed at repair and remyelination.

Primary progressive multiple sclerosis. It is important to include this group in future treatment trials, as they have been relatively neglected to date. Problems in primary progressive multiple sclerosis are a lack of natural history data on the clinical course, and the low sensitivity of MRI to reflect changes over time. A large European Community funded multicentre activity (Magnims) should elucidate aspects of the clinical and MRI natural history (Thompson *et al*., 1997). Probably, the MR protocol should consist of T_2-weighted imaging, plus fast FLAIR imaging to increase sensitivity; fast FLAIR detects an additional 20% of lesions in the subcortical region in primary progressive multiple sclerosis (Gawne-Cain *et al*., 1997). It is also important to collect putative markers of demyelination and axonal loss, given their potential to predict disability more strongly. Gadolinium enhancement is not indicated as few enhancing lesions are seen in this subgroup, even when a triple dose is used (Filippi *et al*., 1995*a*, 1997*b*; Silver *et al*., 1997*a*).

Treating acute relapses. MR monitors of treatments for acute relapse might be the total extent of the residual T_2-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). Lesion extent can be particularly well demonstrated in the optic nerve, and this site has the advantage of allowing excellent clinical and electrophysiological correlations of the evolving MRI lesion. It has already been shown that poor visual recovery in optic neuritis is associated with longer optic nerve lesions, and that intravenous methyl prednisolone does not modify the evolution or final length of the MRI lesion (Kapoor *et al*., 1997).

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. It is possible that reversal of MTR abnormalities may tell us something about remyelination, although other processes such as resolution of oedema and gliosis might contribute. A good deal more correlation between the experimental and human pathology of inflammatory/demyelinating disorders and the new MR markers is required to elucidate the MR–pathology relationship.

Future role of newer MR techniques. Accurate measurement of increasing atrophy shows much potential (Losseff *et al*., 1996*b*), particularly with registration/subtraction techniques on 3D data as succesfully employed in Alzheimer's disease (Fox *et al*., 1996). It will be of interest to apply serial atrophy studies in the brain, spinal cord and optic nerves. Measurement of MTR histograms provides a robust, quantitative measure, and is showing stronger correlations with clinical status in preliminary studies (van Buchem *et al*., 1996*b*).

Proton MR spectroscopy is more technically demanding in terms of time, reproducibility and quantification, and has a low signal-to-noise. It is not yet ready to apply serially beyond the few centres with a highly specialized interest. Similarly, T_2-magnetization decay analysis and diffusion weighted imaging require more developmental work, but are of potential long-term interest. Functional MRI has the potential to look at cortical readaptation mechanisms as an element of the recovery process in multiple sclerosis. High field (4-T) scanners provide an opportunity to increase the resolution of MRI further, and especially to improve the SNR and resolution for spectroscopy. However, very few 4-T machines are currently available, and their long-term applicability is uncertain. Other techniques, such as perfusion MRI and sodium imaging, are of potential interest, but still developmental.

Conclusion

MR techniques provide an objective and direct assessment of the evolving pathology in multiple sclerosis. There is an increasing definition of their pathological specificity, and the problems relating to robust and stable quantification of MR outcomes are being gradually solved. It is likely that MR techniques will become more rather than less important in monitoring treatment efficacy in multiple sclerosis in the coming years.

Acknowledgements

This review is based on the proceedings of an international workshop, entitled 'The Role of Magnetic Resonance

Techniques in Understanding and Managing Multiple Sclerosis', held in Oxford, UK, January 15–19, 1997. The workshop Chairs were: Robert Grossman, MD, PhD (University of Pennsylvania, USA), Henry McFarland, MD (National Institutes of Health, USA); David Miller, MD (Institute of Neurology, UK). The workshop was sponsored by the National Multiple Sclerosis Society (USA) and the International Federation of Multiple Sclerosis Societies; additional support provided by Athena Neurosciences (USA), Autoimmune, Inc. (USA), Berlex Laboratories (USA), Biogen USA, Biogen Europe, Biogen Canada, National Institute of Neurological Disorders and Stroke (USA), Ortho Biotech, Inc. (USA), Schering AG (Germany), Teva Marion Partners (USA), Teva Pharmaceutical Industries, Ltd, Hoechst Marion Roussel (USA). Presentations at the workshop were made by the following participants: W. I. McDonald, R. Grossman, J. Hajnal, T. Yousry, M. Gawne-Cain, J. Frank, M. Filippi, J. McGowan, M. van Buchem, J. van Waesberge, A. MacKay, D. Arnold, N. Losseff, M. Horsfield, C. DeCarli, J. Udupa, H. McFarland, J. Simon, F. Fazekas, D. Li, L. Stone, J. Wolinsky, A. Thompson, S. Rao, C. Polman, H. Weiner, H.-P. Hartung, A. Miller, P. Matthews, L. Kappos, F. Barkhof, P. Tofts, A. J. Petkau, J. Noseworthy, D. Miller, J. Antel, C. Pozzilli, R. Rudick, E. Willoughby and D. W. Paty. We wish to thank W. Weal, National Multiple Sclerosis Society (USA), for organizing the conference.

References

Armspach JP, Gounot D, Rumbach L, Chambron J. In vivo determination of multiexponential T2 relaxation in the brain of patients with multiple sclerosis. Magn Reson Imaging 1991; 9: 107–13.

Arnett PA, Rao SM, Bernardin L, Grafman J, Yetkin FZ, Lobeck L. Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. Neurology 1994; 44: 420–5.

Arnold DL, Matthews PM, Francis G, Antel J. Proton magnetic resonance spectroscopy of human brain in vivo in the evaluation of multiple sclerosis: assessment of the load of disease. Magn Reson Med 1990; 14: 154–9.

Arnold DL, Matthews PM, Francis GS, O'Connor J, Antel JP. Proton magnetic resonance spectroscopic imaging for metabolic characterization of demyelinating plaques. Ann Neurol 1992; 31: 235–41.

Barker GJ, MacManus DG, Bartlett P. 3D fast FLAIR – a CSF-nulled 3D fast spin echo pulse sequence. Proc Int Soc Magn Reson Med 1997; 1: 284.

Barkhof F, Scheltens P, Frequin ST, Nauta JJ, Tas MW, Valk J, et al. Relapsing-remitting multiple sclerosis: sequential enhanced MR imaging vs clinical findings in determining disease activity. AJR Am J Roentgenol 1992; 159: 1041–7.

Barkhof F, Filippi M, Miller DH, Scheltens Ph, Campi A, Polman CH, et al. Comparison of MR imaging criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997. In press.

Barnes D, McDonald WI, Tofts PS, Johnson G, Landon DN. Magnetic resonance imaging of experimental cerebral oedema. J Neurol Neurosurg Psychiatry 1986; 49: 1341–7.

Barnes D, McDonald WI, Landon DN, Johnson G. The characterization of experimental gliosis by quantitative nuclear magnetic resonance imaging. Brain 1988; 111: 83–94.

Bastianello S, Pozzilli C, Bernardi S, Bozzao L, Fantozzi LM, Buttinelli C, et al. Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. Neurology 1990; 40: 591–5.

Beck RW, Cleary PA, Trobe JD, Kaufman DI, Kupersmith MJ, Paty DW, et al. The effect of corticosteriods for acute optic neuritis on the subsequent development of multiple sclerosis [see comments]. N Engl J Med 1993; 329: 1764–9. Comment in: N Engl J Med 1993; 329: 1808–10, Comment in: N Engl J Med 1994; 330: 1238–9. Comment in: ACPJ Club 1994; 120 Suppl 3: 61.

Berry I, Barker G, Barkhof F, Campi A, Dousset V, Franconi JM, et al. A multicentre measurement of magnetisation transfer ratio in normal white matter. Proc Int Soc Magn Reson Med 1996; 1: 536.

Boorstein JM, Wong KT, Grossman RI, Bolinger L, McGowan JC. Metastatic lesions of the brain: imaging with magnetization transfer. Radiology 1994; 191: 799–803.

Brenner RE, Munro PM, Williams SC, Bell JD, Barker GJ, Hawkins CP, et al. The proton NMR spectrum in acute EAE: the significance of the change in the Cho:Cr ratio. Magn Reson Med 1993; 29: 737–45.

Calabresi PA, Tranquill LR, Dambrosia JM, Stone LA, Maloni H, Bash CN, et al. Increases in soluble VCAM-1 correlate with a decrease in MRI lesions in multiple sclerosis treated with interferon beta-1b. Ann Neurol 1997; 41: 669–74.

Charcot JM. Histologie de la sclérose en plaques. Gaz Hôp Paris 1868; 41: 554–5, 557–8, 566.

Davie CA, Hawkins CP, Barker GJ, Brennan A, Tofts PS, Miller DH, et al. Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions. Brain 1994; 117: 49–58.

Davie CA, Barker GJ, Webb S, Tofts PS, Thompson AJ, Harding AE, et al. Persistent functional deficit in multiple sclerosis and autosomal dominant cerebellar ataxia is associated with axon loss [published erratum appears in Brain 1996; 119: 1415]. Brain 1995; 118: 1583–1592.

De Coene B, Hajnal JV, Gatehouse P, Longmore DB, White SJ, Oatridge A, et al. MR of the brain using fluid-attenuated inversion recovery (FLAIR) pulse sequences. AJNR Am J Neuroradiol 1992; 13: 1555–64.

De Coene B, Hajnal JV, Pennock JM, Bydder GM. MRI of the brain stem using fluid attenuated inversion recovery pulse sequences. Neuroradiology 1993; 35: 327–31.

De Stefano N, Matthews PM, Antel JP, Preul M, Francis G, Arnold DL. Chemical pathology of acute demyelinating lesions and its correlation with disability. Ann Neurol 1995; 38: 901–9.

Dousset V, Grossman RI, Ramer KN, Schnall MD, Young LH, Gonzales-Scarano F, et al. Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging [published erratum appears in Radiology 1992; 183: 878]. Radiology 1992; 182: 483–491.

Evans AC, Frank JA, Antel J, Miller DH. The role of MRI in clinical trials of multiple sclerosis: comparison of image processing techniques. Ann Neurol 1997; 41: 125–32.

Fazekas F, Offenbacher H, Fuchs S, Schmidt R, Niederkorn K, Horner S, et al. Criteria for an increased specificity of MRI interpretation in elderly subjects with suspected multiple sclerosis. Neurology 1988; 38: 1822–5.

Feinstein A, Kartsounis LD, Miller DH, Youl BD, Ron MA. Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. J Neurol Neurosurg Psychiatry 1992; 55: 869–76.

Filippi M, Horsfield MA, Morrissey SP, MacManus DG, Rudge P, McDonald WI, et al. Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology 1994; 44: 635–41.

Filippi M, Campi A, Martinelli V, Colombo B, Yousry T, Canal N, et al. Comparison of triple dose versus standard dose gadolinium-DTPA for detection of MRI enhancing lesions in patients with primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 1995a; 59: 540–4.

Filippi M, Paty DW, Kappos L, Barkhof F, Compston DA, Thompson AJ, et al. Correlations between changes in disability and T_2-weighted brain MRI activity in multiple sclerosis. A follow-up study. Neurology 1995b; 45: 255–60.

Filippi M, Yousry T, Baratti C, Horsfield MA, Mammi S, Becker C, et al. Quantitative assessment of MRI lesion load in multiple sclerosis: a comparison of conventional spin-echo with fast fluid-attenuated inversion recovery. Brain 1996a; 119: 1349–55.

Filippi M, Yousry T, Campi A, Kandziora C, Colombo B, Voltz R, et al. Comparison of triple dose versus standard dose gadolinium-DTPA for detection of MRI enhancing lesions in patients with MS. Neurology 1996b; 46: 379–84.

Filippi M, Yousry T, Rocca MA, Fesl G, Comi G. Sensitivity of delayed enhanced MRI in multiple sclerosis. Proc Int Soc Magn Reson Med 1996c; 1: 543.

Filippi M, Rovaris M, Campi A, Pereira C, Comi G. Semi-automated thresholding technique for measuring lesion volumes in multiple sclerosis: effects of the change of the threshold on the computed lesion loads. Acta Neurol Scand 1996d; 93: 30–4.

Filippi M, Yousry TA, Alkadhi H, Stehling M, Horsfield MA, Voltz R. Spinal cord MRI in multiple sclerosis with multicoil arrays: a comparison between fast spin echo and fast FLAIR. J Neurol Neurosurg Psychiatry 1996e; 61: 632–5.

Filippi M, Rovaris M, Sormani MP, Gasperini C, Capra R, Colombo B, et al. A multicentre, longitudinal study comparing the sensitivity of monthly enhanced MRI after single and triple dose Gd-DTPA injection for monitoring disease activity in multiple sclerosis. Proc Int Soc Magn Reson Med 1997a; 1: 71.

Filippi M, Yousry T, Fesl G, Voltz R, Rovaris M, Rocca MA. Triple dose of Gd-DTPA markedly increases the sensitivity of spinal cord MRI for detecting enhancing lesions in multiple sclerosis. Proc Int Soc Magn Reson Med 1997b; 1: 430.

Fox NC, Freeborough PA, Rossor MN. Visualisation and quantification of rates of atrophy in Alzheimer's disease [see comments]. Lancet 1996; 348: 94–7. Comment in: Lancet 1996; 348: 829–8.

Fralix TA, Ceckler TL, Wolff SD, Simon SA, Balaban RS. Lipid bilayer and water proton magnetization transfer:effect of cholesterol. Magn Reson Med 1991; 18: 214–23.

Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design [see comments]. Stat Med 1992; 11: 1685–704. Comment in: Stat Med 1994; 13: 197–8.

Gasperini C, Horsfield MA, Thorpe JW, Kidd D, Barker GJ, Tofts PS, et al. Macroscopic and microscopic assessments of disease burden by MRI in multiple sclerosis: relationship to clinical parameters. J Magn Reson Imaging 1996; 6: 580–4.

Gass A, Barker GJ, Kidd D, Thorpe JW, MacManus D, Brennan A, et al. Correlation of magnetization transfer ratio with clinical disability in multiple sclerosis. Ann Neurol 1994; 36: 62–7.

Gawne-Cain ML, O'Riordan JI, Thompson AJ, Moseley IF, Miller DH. Multiple sclerosis lesion detection in the brain: a comparison of fast fluid attenuated inversion recovery and conventional T2 weighted dual spin echo. Neurology 1997; 49: 364–70

Gersonde K, Tolxdorff T, Felsberg L. Identification and characterization of tissues by T2-selective whole-body proton NMR imaging. Magn Reson Med 1985; 2: 390–401.

Giovannoni G, Thorpe JW, Kidd D, Kendall BE, Moseley IF, Thompson AJ, et al. Soluble E-selectin in multiple sclerosis: raised concentrations in patients with primary progressive disease. J Neurol Neurosurg Psychiatry 1996; 60: 20–6.

Gonzalez CF, Swirsky-Sacchetti T, Mitchell D, Lublin FD, Knobler RL, Ehrlich SM. Distributional patterns of multiple sclerosis brain lesions. J Neuroimaging 1994; 4: 188–95.

Grimaud J, Lai M, Thorpe J, Adeleine P, Wang L, Barker GJ, et al. Quantification of MRI lesion load in multiple sclerosis: a comparison of three computer-assisted techniques. Magn Reson Imaging 1996; 14: 495–505.

Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberberg DH. Multiple sclerosis: gadolinium enhancement in MR imaging. Radiology 1986; 161: 721–5.

Grossman RI, Lenkinski RE, Ramer KN, Gonzales-Scarano F, Cohen JA. MR proton spectroscopy in multiple sclerosis. AJNR Am J Neuroradiol 1992; 13: 1535–43.

Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF. Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. Ann Neurol 1991; 29: 548–55.

Hartung H-P, Reiners K, Archelos JJ, Michels M, Seeldrayers P. Heidenreich F, et al. Circulating adhesion molecules and tumor

necrosis factor receptor in multiple sclerosis: correlation with magnetic resonance imaging. Ann Neurol 1995; 38: 186–93.

Hiehle JF Jr, Lenkinski RE, Grossman RI, Dousset V, Ramer KN, Schnall MD, et al. Correlation of spectroscopy and magnetization transfer imaging in the evaluation of demyelinating lesions and normal appearing white matter in multiple sclerosis. Magn Reson Med 1994; 32: 285–93.

Hiehle JF Jr, Grossman RI, Ramer KN, Gonzales-Scarano F, Cohen JA. Magnetization transfer effects in MR-detected multiple sclerosis lesions: comparison with gadolinium-enhanced spin-echo images and nonenhanced T1-weighted images. AJNR Am J Neuroradiol 1995; 16: 69–77.

Hirsch JA, Lenkinski RE, Grossman, RI. MR spectroscopy in the evaluation of enhancing lesions in the brain in multiple sclerosis. AJNR Am J Neuroradiol 1996; 17: 1829–36.

Horsfield MA, Lai M, Webb SL, Barker GJ, Tofts PS, Turner R, et al. Apparent diffusion coefficients in benign and secondary progressive multiple sclerosis by nuclear magnetic resonance. Magn Reson Med 1996; 36: 393–400.

IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial [see comments]. Neurology 1995; 45: 1277–85. Comment in: ACPJ Club 1996; 124: 3, Comment in: Neurology 1996; 47: 1110–2.

Isaacs C, Li DK, Genton M, Jardine C, Grochowski E, Palmer M, et al. Multiple sclerosis: a serial study using MRI in relapsing patients. Neurology 1988; 38: 1511–5.

Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis [see comments]. Ann Neurol 1996; 39: 285–294. Comment in: ACPJ Club 1996; 125: 35, Comment in: Ann Neurol 1996; 40: 951–3, Comment in: Ann Neurol 1997; 41: 560.

Jacobson JT, Deppe U, Murray TJ. Dichotic paradigms in multiple sclerosis. Ear Hear 1983; 4: 311–7.

Jones SJ. Visual evoked potentials after optic neuritis. Effect of time interval, age and disease dissemination. J Neurol 1993; 240: 489–94.

Kapoor R, Miller DH, Jones SJ, Plant GT, Brusa A, Gass A, et al. Effects of methylprednisolone on outcome in MRI-based prognostic subgroups in acute optic neuritis. Neurology 1997. In press.

Kidd D, Thorpe JW, Thompson AJ, Kendall BE, Moseley IF, MacManus DG, et al. Spinal cord MRI using multi-array coils and fast spin echo. II. Findings in multiple sclerosis. Neurology 1993; 43: 2632–7.

Kidd D, Thorpe JW, Kendall BE, Barker GJ, Miller DH, McDonald WI, et al. MRI dynamics of brain and spinal cord in progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 1996; 60: 15–9.

Kidd D, Barker GJ, Tofts PS, Gass A, Thompson AJ, McDonald WI, et al. The transverse magnetisation decay characteristics of long standing lesions and normal appearing white matter in multiple sclerosis. J Neurol 1997; 244: 125–30.

Kieper MA, Grossman RI, Schnall MD. The low sensitivity of fluid attenuated inversion recovery (FLAIR) imaging in the detection of multiple sclerosis of the spinal cord. AJNR Am J Neuroradiol 1997; 18: 1035–39.

Kimura H, Grossman RI. Lenkinski RE, Gonzales-Scarano F. Proton MR spectroscopy and magnetization transfer ratio in multiple sclerosis: correlative findings in active versus irreversible plaque disease. AJNR Am J Neuroradiol 1996; 17: 1539–47.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444–52.

Lai M, Hodgson T, Gawne-Cain M, Webb S, MacManus D, McDonald WI, et al. A preliminary study into the sensitivity of disease activity detection by serial weekly magnetic resonance imaging in multiple sclerosis. J Neurol Neurosurg Psychiatry 1996; 60: 339–41.

Larsson HB, Frederiksen J, Kjaer L, Henriksen O, Olesen J. In vivo determination of T1 and T2 in the brain of patients with severe but stable multiple sclerosis. Magn Reson Med 1988; 7: 43–55.

Le Bihan D, Turner R, Douek P, Patronas N. Diffusion MR imaging: clinical applications. [Review]. AJR Am J Roentgenol 1992; 159: 591–9.

Lexa FJ, Grossman RI, Rosenquist AC. MR of wallerian degeneration in the feline visual system: characterization by magnetization transfer rate with histopathologic correlation. AJNR Am J Neuroradiol 1994; 15: 201–12.

Loevner LA, Grossman RI, McGowan JC, Ramer KN, Cohen JA. Characterization of multiple sclerosis plaques with T1-weighted MR and quantitative magnetization transfer. AJNR Am J Neuroradiol 1995a; 16: 1473–9.

Loevner LA, Grossman RI, Cohen JA, Lexa FJ, Kessler D, Kolson DL. Microscopic disease in normal-appearing white matter on conventional MR images in patients with multiple sclerosis: assessment with magnetization-transfer measurements. Radiology 1995b; 196: 511–5.

Losseff NA, Webb SL, O'Riordan JI, Page R, Wang L, Barker GJ, et al. Spinal cord atrophy and disability in multiple sclerosis: a new reproducible and sensitive MRI method with potential to monitor disease progression. Brain 1996a; 119: 701–8.

Losseff NA, Wang L, Lai HM, Yoo DS, Gawne-Cain ML, McDonald WI, et al. Progressive cerebral atrophy in multiple sclerosis. A serial MRI study. Brain 1996b; 119: 2009–19.

MacKay A, Whittall KP, Adler J, Li D, Paty D, Graeb D. In vivo visualization of myelin water in brain by magnetic resonance. Magn Reson Med 1994; 31: 673–7.

McDonald WI. The effects of experimental demyelination on conduction in peripheral nerve: a histological and electrophysiological study. II. Electrophysiological observations. Brain 1963; 86: 501–24.

McDonald WI. The pathophysiology of multiple sclerosis. In: Compston A, Ebers G, Lassmann H, McDonald I, Matthews B,

Wekerle H, editors. McAlpine's multiple sclerosis. 3rd ed. Edinburgh: Churchill Livingstone 1997. In press.

McDonald WI, Sears TA. Focal experimental demyelination in the central nervous system. Brain 1970; 93: 575–82.

McFarland HF, Frank JA, Albert PS, Smith ME, Martin R, Harris JO, et al. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. Ann Neurol 1992; 32: 758–66.

Menon RS, Allen PS. Application of continuous relaxation time distributions to the fitting of data from model systems and excised tissue. Magn Reson Med 1991; 20: 214–27.

Miller DH, Newton MR, van der Poel JC, du Boulay EP, Halliday AM, Kendall BE, et al. Magnetic resonance imaging of the optic nerve in optic neuritis. Neurology 1988a; 38: 175–9.

Miller DH, Rudge P, Johnson G, Kendall BE, MacManus DG, Moseley IF, et al. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. Brain 1988b; 111: 927–39.

Miller DH, Barkhof F, Nauta JJ. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. Brain 1993; 116: 1077–94.

Miller DH, Albert PS, Barkhof F, Francis G, Frank JA, Hodgkinson S, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Ann Neurol 1996; 39: 6–16.

Moll C, Mourre C, Lazdunski M, Ulrich J. Increase of sodium channels in demyelinated lesions of multiple sclerosis. Brain Res 1991; 556: 311–6.

Morrissey SP, Miller DH, Kendall BE, Kingsley DP, Kelly MA, Francis DA, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. Brain 1993; 116: 135–46.

Mulkern RV, Bleier AR, Adzamli IK, Spencer RG, Sandor T, Jolesz FA. Two-site exchange revisited: a new method for extracting exchange parameters in biological systems. Biophys J 1989; 55: 221–32.

Nauta JJ, Thompson AJ, Barkhof F, Miller DH. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis patients: statistical power of parallel-groups and crossover designs. J Neurol Sci 1994; 122: 6–14.

Norbash AM, Glover GH, Enzmann DR. Intracerebral lesion contrast with spin-echo and fast spin-echo pulse sequences. Radiology 1992; 185: 661–5.

O'Riordan JI, Losseff N, Thompson AJ, Miller DH. Asymptomatic spinal cord lesions in clinically isolated optic neuritis or brain stem syndromes [abstract]. J Neurol 1996a; 243 Suppl 2: S18.

O'Riordan JI, Thompson AJ, Rudge P, McDonald WI, Miller DH. The long term risk of multiple sclerosis following clinically isolated syndromes of the central nervous system [abstract]. J Neurol 1996b; 243 Suppl 2: S33.

Ormerod IE, Miller DH, McDonald WI, du Boulay EP, Rudge P, Kendall BE, et al. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. Brain 1987; 110: 1579–616.

Pannizzo F, Stallmeyer MJ, Friedman J, Jennis RJ, ZabriskieJ, Plank C, et al. Quantitative MRI studies for assessment of multiple sclerosis. Magn Reson Med 1992; 24: 90–9.

Paty DW, Oger JJ, Kastrukoff LF, Hashimoto SA, Hooge JP, Eisen AA, et al. MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology 1988; 38: 180–5.

Paty DW, Li DK, UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial [see comments]. Neurology 1993; 43: 662–667. Comment in: Neurology 1993; 43: 641–3.

Paty DW, Li DK, Oger JJ, Kastrukoff L, Koopmans R, Tanton E, et al. Magnetic resonance imaging in the evaluation of clinical trials in multiple sclerosis. Ann Neurol 1994; 36 Suppl: S95-6.

Petkau AJ. Statistical and design considerations for multiple sclerosis clinical trials. In: Goodkin DE, Rudick RA, editors. Treatment of Multiple sclerosis: trial design, results, and future strategies. London: Springer-Verlag, 1996, 63–103.

Plummer DL. Dispimage: a display and analysis tool for medical images. Riv Neuroradiol 1992; 5: 489–95.

Poon CS, Henkelman RM. Practical T2 quantitation for clinical applications. J Magn Reson Imaging 1992; 2: 541–53.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227–31.

Prineas JW, Connell F. Remyelination in multiple sclerosis. Ann Neurol 1979; 5: 22–31.

Prineas JW, Barnard RO, Kwon EE, Sharer LR, Cho E-S. Multiple sclerosis: remyelination of nascent lesions. Ann Neurol 1993; 33: 137–51.

Rao SM, Bernardin L, Leo GJ, Ellington L, Ryan SB, Burg LS. Cerebral disconnection in multiple sclerosis: relationship to atrophy of the corpus callosum. Arch Neurol 1989; 46: 918–920.

Richards TL. Proton MR spectroscopy in multiple sclerosis: value in establishing diagnosis, monitoring progression, and evaluating therapy. [Review]. AJR Am J Roentgenol 1991; 157: 1073–1078.

Rovaris M, Yousry T, Calori G, Fesl G, Volz R, Filippi M. Fast-FLAIR, FSE and TGSE sequences in the assessment of brain MRI lesion load in multiple sclerosis: a preliminary study. J Neuroimaging 1997a. In press.

Rovaris M, Gawne-Cain ML, Wang L, Miller DH. A comparison of conventional and fast spin-echo sequences for the measurement of lesion load in multiple sclerosis using a semi-automated contour technique. Neuroradiology 1997b; 39: 161–5.

Rubens AB, Froehling B, Slater G, Anderson D. Left ear suppression on verbal dichotic tests in patients with multiple sclerosis. Ann Neurol 1985;18: 459–63.

Rudick R, Antel J, Confavreux C, Cutter G, Ellison G, Fischer J, et al. Clinical outcomes assessment in multiple sclerosis. [Review]. Ann Neurol 1996; 40: 469–79.

Rumbach L, Armspach JP, Gounot D, Namer IJ, Chambron J, Warter J-M, et al. Nuclear magnetic resonance T2 relaxation times in multiple sclerosis. J Neurol Sci 1991; 104: 176–81.

Rydberg JN, Hammond CA, Grimm RC, Erickson BJ, Jack CR Jr, Huston J 3rd, et al. Initial clinical experience in MR imaging of the brain with a fast fluid-attenuated inversion-recovery pulse sequence. Radiology 1994; 193: 173–80.

Silver NC, Good CD, Barker GJ, MacManus DG, Thompson AJ, Moseley IF, et al. Sensitivity of contrast enhanced MRI in multiple sclerosis. Effects of gadolinium dose, magnetisation transfer contrast and delayed imaging. Brain 1997a; 120: 1749–61.

Silver NC, Barker GJ, Losseff NA, Gawne-Cain, MacManus DG, Thompson AJ, et al. Magnetization transfer ratio measurement in the cervical spinal cord. A preliminary study in multiple sclerosis. Neuroradiology 1997b; 39: 441–5.

Simmons ML, Frondoza CG, Coyle JT. Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. Neuroscience 1991; 45: 37–45.

Simon JH, Scherzinger A, Raff U, Li X. Computerized method of serial lesion volume quantitation in multiple sclerosis: error of serial studies. AJNR Am J Neuroradiol 1997; 18: 580–2.

Smith ME, Stone LA, Albert PS, Frank JA, Martin R, Armstrong M, et al. Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. Ann Neurol 1993; 33: 480–9.

Stevenson VL, Gawne-Cain ML, Barker GJ, Thompson AJ, Miller DH. Imaging of the spinal cord and brain in multiple sclerosis: a comparative study between fast FLAIR and fast spin echo. J Neurol 1997; 244: 119–24.

Stewart WA, Hall LD, Berry K, Paty DW. Correlation between NMR scan and brain slice data in multiple sclerosis [letter]. Lancet 1984; 2: 412.

Stone LA, Frank JA, Albert PS, Bash C, Smith ME, Maloni H, et al. The effect of interferon-beta on blood-brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. Ann Neurol 1995; 37: 611–9.

Stuber A, Martin R, Stone LA, Maloni H, McFarland HF. Expression pattern of activation and adhesion molecules on peripheral blood CD4+ T-lymphocytes in relapsing-remitting multiple sclerosis patients: a serial analysis. J Neuroimmunol 1996; 66: 147–51.

Swirsky-Sacchetti T, Mitchell DR, Seward J, Gonzales C, Lublin F, Knobler R, et al. Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis. Neurology 1992; 42: 1291–5.

Thompson AJ, Kermode AG, Wicks D, MacManus DG, Kendall BE, Kingsley DP, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. Ann Neurol 1991; 29: 53–62.

Thompson AJ, Miller D, Youl B, MacManus D, Moore S, Kingsley D, et al. Serial gadolinium-enhanced MRI in relapsing/remitting multiple sclerosis of varying disease duration. Neurology 1992; 42: 60–3.

Thompson AJ, Polamn C, Miller DH, Brochet B, Filippi M, Montalban X, et al. Primary progressive multiple sclerosis: a review. Brain 1997; 120: 1085–96.

Thorpe JW, Halpin SF, MacManus DG, Barker GJ, Kendall BE, Miller DH. A comparison between fast and conventional spin-echo in the detection of multiple sclerosis lesions. Neuroradiology 1994; 36: 388–92.

Thorpe JW, Kidd D, Moseley IF, Thompson AJ, MacManus DG, Compston DA, et al. Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI. Brain 1996a; 119: 709–14.

Thorpe JW, Kidd D, Moseley IF, Kendall BE, Thompson AJ, MacManus DG, et al. Serial gadolinium-enhanced MRI of the brain and spinal cord in early relapsing-remitting multiple sclerosis. Neurology 1996b; 46: 373–8.

Truyen L, van Waesberghe JH, van Walderveen MA, van Oosten BW, Polman CH, Hommes OR, et al. Accumulation of hypointense lesions ('black holes') on T_1 spin-echo MRI correlates with disease progression in multiple sclerosis. Neurology 1996; 47: 1469–76.

Tubridy N, Ader H, Barkhof F, Thompson AJ, Miller DH. Sample size calculations for MRI outcome pilot trials in multiple sclerosis: relapsing-remitting versus secondary progressive subgroups [abstract]. Neurology 1997; 48 (3 Suppl 2): A175.

Udupa JK, Wei L, Samarasekera S, Miki Y, van Buchem MA, Grossman RI. Multiple sclerosis lesion quantification using fuzzy connectedness principles. IEEE Trans Med Imag 1997. In press.

Uhlenbrock D, Sehlen S. The value of T1-weighted images in the differentiation between MS, white matter lesions, and subcortical arteriosclerotic encephalopathy (SAE). [Review]. Neuroradiology 1989; 31: 203–12.

van Buchem MA, McGowan JC, Kolson DL, Polansky M, Grossman RI. Quantitative volumetric magnetization transfer analysis in multiple sclerosis: estimation of macroscopic and microscopic disease burden. Magn Reson Med 1996a; 36: 632–6.

van Buchem MA, Grossman RI, Miki Y, Udupa JK, Polansky M, McGowan JC. Correlation of quantitative volumetric magnetization transfer ratio measurements with clinical and neuropsychological data in multiple sclerosis [abstract]. Radiology 1996b; 201(P) Suppl: 174–5.

van Walderveen MA, Barkhof F, Hommes OR, Polman CH, Tobi H, Frequin ST, et al. Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR/short-TE (T1-weighted) spin-echo images. Neurology 1995; 45: 1684–90.

van Walderveen MA, Scheltens P, Barkhof F, Ravid R, Polman CH, Valk J, et al. Histopatholgic correlates of hypointense lesions on T1-weighted SE MR images in multiple sclerosis [abstract]. J Neurol 1996; 243 Suppl 2: S18.

Whitaker JN, McFarland HF, Rudge P, Reingold SC. Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. Multiple Sclerosis 1995; 1: 37–47.

White SJ, Hajnal JV, Young IA, Bydder GM. Use of fluid-attenuated inversion-recovery pulse sequences for imaging the spinal cord. Magn Reson Med 1992; 28: 153–62.

Wicks DA, Tofts PS, Miller DH, du Boulay GH, Feinstein A, Sacares RP, et al. Volume measurement of multiple sclerosis lesions with magnetic resonance images: a preliminary study. Neuroradiology 1992; 34: 475–9.

Willoughby EW, Grochowski E, Li DK, Oger J, Kastrukoff LF, Paty DW. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. Ann Neurol 1989; 25: 43–9.

Wolff SD, Balaban RS. Magnetization transfer imaging: practical aspects and clinical applications. [Review]. Radiology 1994; 192: 593–9.

Wolinsky JS, Narayana PA, Fenstermacher MJ. Proton magnetic resonance spectroscopy in multiple sclerosis. Neurology 1990; 40: 1764–9.

Youl BD, Turano G, Miller DH, Towell AD, MacManus DG, Moore SG, et al. The pathophysiology of acute optic neuritis. Brain 1991; 114: 2437–50.

Received June 6, 1997. Revised August 15, 1997.
Accepted August 15, 1997