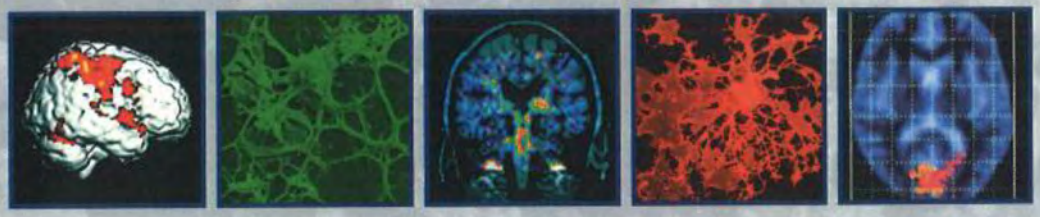
Fourth Edition

McAlpine's MULTIPLE SCLEROSIS



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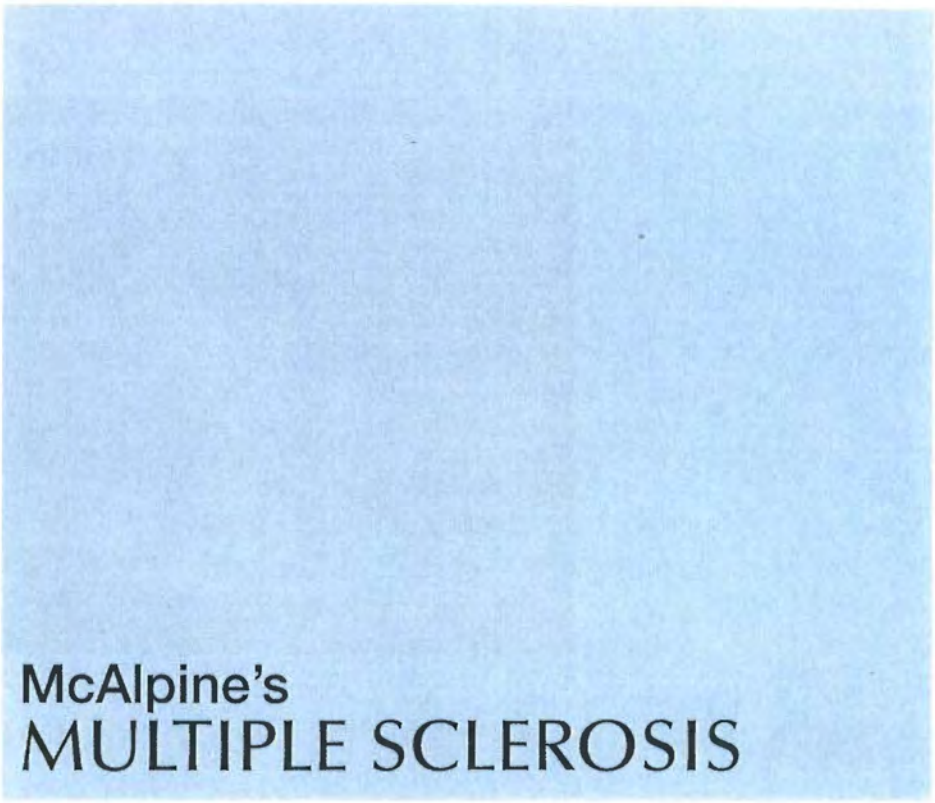
McAlpine's
MULTIPLE SCLEROSIS

For NDC (1918–1986)

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McAlpine's MULTIPLE SCLEROSIS

FOURTH EDITION

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7 The diagnosis of multiple sclerosis

David Miller, Ian McDonald and Kenneth Smith

DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

Given the lack of a specific laboratory test for multiple sclerosis, the only certain means of proving the diagnosis is histological examination of tissue obtained from multiple sites within the central nervous system. The neurologist confronted with a patient in whom the diagnosis of multiple sclerosis is suspected must answer a number of questions:

- Is the history compatible?
- Are there multiple lesions in the central nervous system?
- Are the lesions demyelinating in nature?
- Is there an immunological abnormality in relation to the central nervous system?
- Does an alternative and more likely explanation for the clinical and investigative picture seem likely?

In some cases, the clinical picture alone may be sufficient to establish the diagnosis with considerable confidence. Even then, the neurologist often seeks the reassurance of confirmatory results from laboratory investigations, especially when treatments carrying known or unknown risks of long-term adverse effects are being contemplated. However, there is often genuine diagnostic uncertainty, especially early in the course of the disease. A number of schemes for assigning relative certainty to the diagnosis have been used over the years. At first they were based on clinical features alone but, in 1983, a distinguished group of neurologists reached consensus on a classification that, although retaining some weaknesses, gained widespread acceptance in clinical practice, epidemiology and treatment trials (Table 7.1; C.M. Poser *et al* 1983). The Poser criteria had as their gold standard for the diagnosis of multiple sclerosis two or more attacks affecting two or more necessarily separate sites within the central nervous system (including one or other optic nerves) but, for clinically definite disease, also allowed clinical evidence to be replaced by laboratory abnormalities at the second site. Imaging, electrophysiology and cerebrospinal fluid examination were used to supplement evidence for the diagnosis in situations where clinical criteria were not met, either through absence of the second clinical episode or affected site. Not every patient fitted neatly into this classification and the patients with progressive disease proved especially difficult to evaluate. McAlpine *et al* (1955) had distinguished patients in whom a single episode is followed some years later by progressive disease and called these transitional progressive cases. This category was largely ignored but Gayou *et al* (1997) showed that, amongst 214 consecutively presenting patients, 12 had transitional multiple sclerosis compared with 38 with primary and 55 with secondary progressive disease. Serial assessments of clinical activity and magnetic resonance imaging (MRI) confirmed that transitional progressive multiple sclerosis behaves more like primary than secondary progressive disease.

The issue of working definitions for primary progressive multiple sclerosis was finally tackled by A.J. Thompson *et al* (2000) who argued that there should be clinical progression for at least 1 year and that three levels of diagnostic certainty could be defined – based on a consideration of the findings from cerebrospinal fluid examination, MRI and evoked potentials. To make a definite diagnosis according to these criteria, there must be oligoclonal bands present in the cerebrospinal fluid. In addition, it is required that there is either 'definite' MRI abnormality (that is nine or more brain lesions; or two or more spinal cord lesions; or one spinal cord lesion plus four to eight brain lesions), or 'equivocal' (that is, lesser degrees of) MRI abnormality together with a delayed visual evoked response. In essence, the categories of probable and possible primary progressive multiple sclerosis require lesser degrees of abnormality within this spectrum of potentially informative laboratory investigations (A.J. Thompson *et al* 2000).

Against this background, new criteria have been proposed both for clinical and research purposes. One guiding principle was to bring forward the point at which the diagnosis of multiple sclerosis can be made with sufficient security, in the interests of informed discussions with individual patients, and as the basis for taking decisions on the use of disease-modifying treatments early in the disease course when these are most likely to be useful. The other purpose was to make best use of the accumulated evidence on the predictive value – sensitivity and specificity – of laboratory investigations introduced since 1983, whilst still recognizing that these methods are not universally available or performed to comparable standards (Tables 7.2–7.4 and Figure 7.1) These new criteria, developed by an International Panel, have generally been well accepted (W.I. McDonald *et al* 2001). The main change is that specific MRI features for dissemination in time and space are now incorporated. Thus, if a patient has a single clinical episode characteristic of demyelination accompanied by signs only of the

Table 7.1 Poser criteria for the diagnosis of multiple sclerosis

Category	Attacks	Clinical evidence	Paraclinical evidence	CSF OB/IgG
A. Clinically definite multiple sclerosis				
CDMS A1	2	2		
CDMS A2	2	1	and 1	
B. Laboratory-supported definite multiple sclerosis				
LSDMS B1	2	1	or 1	+
LSDMS B2	1	2		+
LSDMS B3	1	1	and 1	+
C. Clinically probable multiple sclerosis				
CPMS C1	2	1		
CPMS C2	1	2		
CPMS C3	1	1	and 1	
D. Laboratory-supported probable multiple sclerosis				
LSPMS D1	2			+

CSF, cerebrospinal fluid; OB, oligoclonal band; IgG, immunoglobulin G.
From C.M. Poser et al *(1983) with permission.*

Table 7.3 McDonald criteria for multiple sclerosis: MRI evidence for dissemination in space

Three of the following:

- one or more gadolinium enhancing lesions or nine or more T_2 hyperintense lesions if there is no gadolinium enhancing lesion
- one or more infratentorial lesions
- one or more juxtacortical lesions
- three or more periventricular lesions

Notes: (i) one spinal cord lesion can substitute for one brain lesion; (ii) two T_2 lesions plus cerebrospinal fluid oligoclonal bands also constitute evidence for dissemination in space.
From W.I. McDonald et al *(2001) with permission.*

Table 7.4 McDonald criteria for multiple sclerosis: MRI evidence for dissemination in time.

1. If a first scan is >3 months after the onset of the clinical event, the presence of a gadolinium enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T_2 or gadolinium enhancing scan at this time then fulfils the criterion for dissemination in time.

2. If the first scan is performed <3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan ≥3 months after the first scan that shows a new T_2 or gadolinium enhancing lesion will suffice.

From W.I. McDonald et al *(2001) with permission.*

Table 7.2 McDonald criteria for multiple sclerosis: categories of multiple sclerosis

Clinical presentation	Additional data needed for diagnosis of multiple sclerosis
Two or more attacks; objective clinical evidence of two or more lesions	None[a]
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space demonstrated by MRI[b] or Up to two MRI detected lesions consistent with multiple sclerosis plus positive cerebrospinal fluid[c] or Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	Dissemination in time demonstrated by MRI[d] or Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space demonstrated by MRI[b] or Up to two MRI detected lesions consistent with multiple sclerosis plus positive cerebrospinal fluid[c] and Dissemination in time demonstrated by MRI[d] or Second clinical attack
Insidious neurological progression suggestive of multiple sclerosis	Positive cerebrospinal fluid[c] and Dissemination in space demonstrated by: (i) nine or more T_2 lesions in the brain or (ii) two or more lesions in the spinal cord or (iii) four to eight brain lesions plus one spinal cord lesion or Abnormal visual evoked potential[e] associated with four to eight brain lesions, or with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI and Dissemination in time demonstrated by MRI[d] or Continued progression for 1 year

a No additional tests are required (however, if MRI and cerebrospinal fluid are undertaken and are negative extreme caution should be taken before making a diagnosis of multiple sclerosis. Alternative diagnoses must be considered and there must be no better explanation for the clinical picture).
b Must fulfil the Barkhof/Tintoré criteria (Table 7.3).
c Positive cerebrospinal fluid established by oligoclonal bands detected by established methods (preferably isoelectric focusing) different from any such bands in serum or by a raised immunoglobulin G index.
d Must fulfil the criteria in Table 7.4.
e Abnormal visual evoked potential of the type seen in multiple sclerosis (delay with well-preserved wave form).
From W.I. McDonald et al *(2001) with permission.*

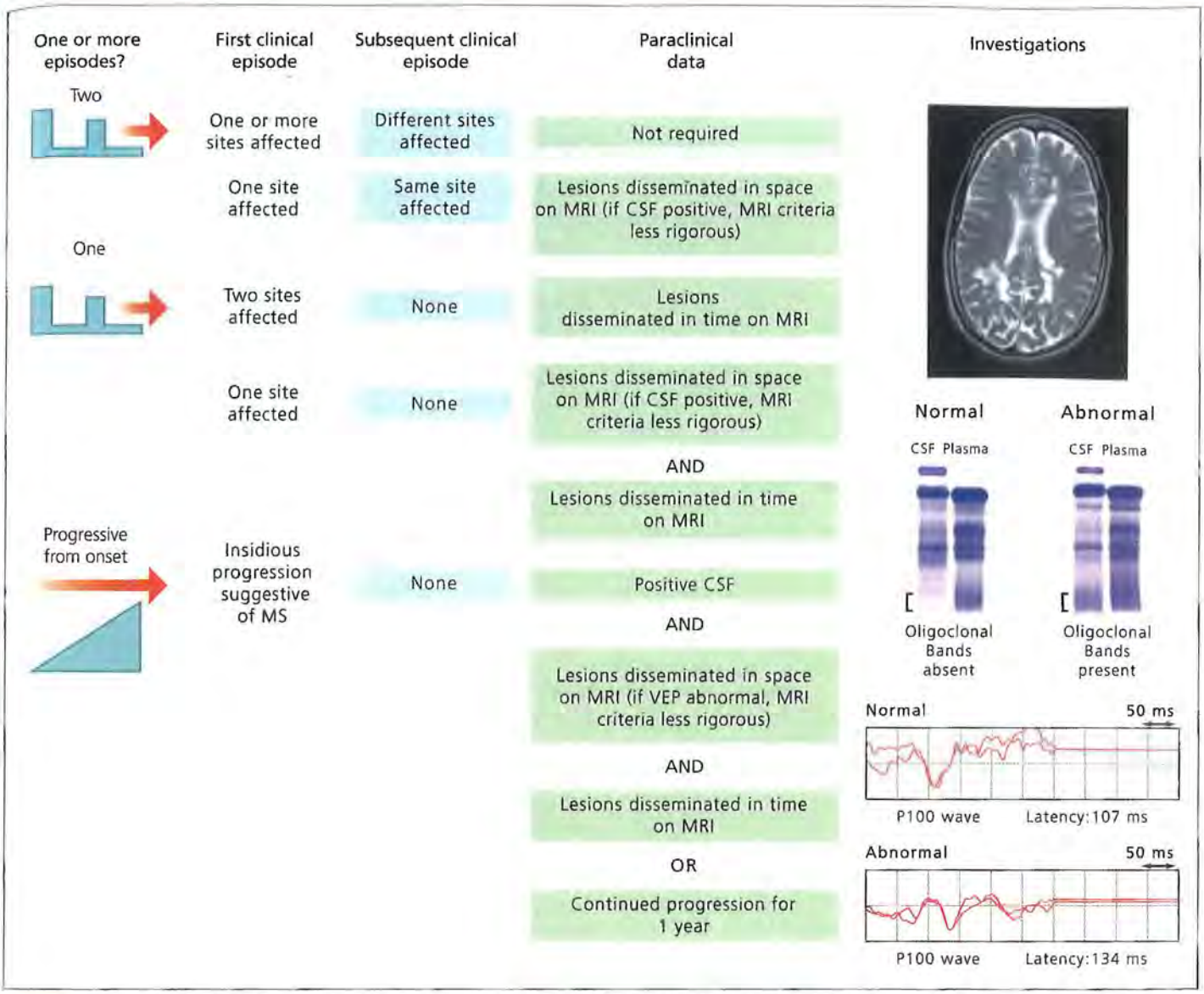


Figure 7.1 The principle is to establish that two or more episodes affecting separate sites within the central nervous system have occurred at different times, using clinical analysis or laboratory investigations. Patients with an appropriate clinical presentation, but who do not meet all of the diagnostic criteria may be classified as having 'possible multiple sclerosis'. CSF, cerebrospinal fluid; VEP, visual evoked potential. Adapted from Compston and Coles (2002).

symptomatic lesion on examination, the demonstration by MRI of dissemination in time and space allows a diagnosis of multiple sclerosis. If the patient with a single attack has signs of two lesions on examination, MRI evidence for dissemination in time will satisfy the diagnosis of multiple sclerosis. If a patient has two clinical episodes suggestive of demyelination (as with the previous Poser criteria, it is required that at least 30 days separates the two events) but signs of only one lesion on examination, MRI evidence for dissemination in space will achieve a diagnosis of multiple sclerosis. In a patient who has two relapses and signs of two lesions on examination, MRI is not required for diagnosis, as was the case for the Poser criteria (such cases were then designated as clinically definite multiple sclerosis).

The MRI features of dissemination in space in the new criteria have evolved from the previous efforts of several imaging research groups to increase the specificity of MRI findings for multiple sclerosis (Barkhof *et al* 1997a; Fazekas *et al* 1988; D.W. Paty *et al* 1988; Tintoré *et al* 2000). At an early stage, Fazekas *et al* (1988) suggested that support for the diagnosis of multiple sclerosis provided by T_2-weighted MRI required the presence of three or more lesions *and* two of the following three features:

- areas of abnormal signal with a diameter of ≥6 mm
- areas of abnormal signal abutting the bodies of the ventricles
- areas of abnormal signal in the infratentorial region.

Subsequently, Barkhof *et al* (1997a) analysed the use of multiple individual features of brain MRI lesions in determining which combination in a multifactorial model was best able to predict conversion from a clinically isolated syndrome to multiple sclerosis. After a mean follow-up of 3 years, they identified

a high predictive value for conversion when four features were present:

- one or more gadolinium enhancing lesions
- three or more periventricular lesions
- one or more juxtacortical lesions
- one or more infratentorial lesions.

Tintoré *et al* (2000) proposed a modification of these Barkhof criteria, limiting the requirement to any three of the four features, and substituting the need for one gadolinium enhancing lesion with the alternative of at least nine T_2 lesions. The combined criteria of Barkhof modified by Tintore were adopted by the International Panel as evidence for dissemination in space (W.I. McDonald *et al* 2001; Table 7.3). The Panel included two additional items in its dissemination in space criteria. First, one spinal cord lesion can substitute for one brain lesion. Second, the criteria are satisfied by the combination of two T_2 lesions together with the presence of oligoclonal bands in the cerebrospinal fluid.

The key feature for MRI dissemination in time using these revised criteria is that a new lesion should appear at least 3 months after the clinical onset. This could be a gadolinium enhancing lesion on any scan obtained 3 or more months after clinical onset or, if such a scan does not show any enhancing lesions, the presence of a new T_2 lesion on a subsequent scan will suffice.

The new criteria recommend that they are best applied to individuals aged between 10 and 59 years. They also no longer include the categories of clinically definite or probable multiple sclerosis. Rather, the diagnostic categories are:

- multiple sclerosis – when the criteria are met
- possible multiple sclerosis – for those at risk of multiple sclerosis but for whom diagnostic evaluation is equivocal
- not multiple sclerosis.

Preliminary studies have attempted to validate the new criteria in terms of specificity and predictive value for development of clinically definite multiple sclerosis (discussed below). The criteria have both strengths and weaknesses and these are discussed further in Chapter 9. They are likely to be revised and fine tuned as more experience is gained of their application and indeed modifications to the criteria are expected following the meeting on a reconstituted International Panel in March 2005. Here, we consider the contribution that special or paraclinical investigations can make to the diagnostic process, but start by reiterating that, as in all branches of clinical neurology, laboratory investigations should never replace a full evaluation of the history and clinical examination when seeking to establish the diagnosis.

SELECTION OF INVESTIGATIONS

Three types of investigation may be needed in patients suspected of having demyelinating disease: MRI, evoked potentials and cerebrospinal fluid examination. Their purpose is to document the dissemination of lesions in space and time; to confirm the presence of intrathecal inflammation; and to exclude conditions that mimic demyelination. The starting point for diagnosis in the individual patient is the clinical picture. More than any other feature, this determines the nature and number of investigations required to reach the appropriate level of diagnostic certainty. In essence, the neurologist must ask the questions: which parts of the nervous system should I investigate; and how best can this be achieved?

The diagnosis of multiple sclerosis cannot by definition be made on clinical grounds alone, if there has been only a single episode (for example, optic neuritis). However, the risk of disseminated disease developing later may be estimated from MRI, evoked potentials and cerebrospinal fluid data (see below). Making use of their predictive values may have therapeutic implications, especially as treatments that safely delay the progression of disability are increasingly made available. By applying the most recently published authoritative criteria, such paraclinical investigations can be used to make a diagnosis of multiple sclerosis 3 months after symptom onset (W.I. McDonald *et al* 2001).

A commonly encountered problem is the patient who has had several episodes of neurological symptoms suggestive of multiple sclerosis, but who, on examination, has abnormal signs relating only to the most recent event. In these circumstances, MRI, or occasionally evoked potentials, reveals whether the nervous system has been involved at other sites even though these have not given rise to clinical manifestations. In selecting the parts of the nervous system that should be examined to demonstrate dissemination in space, the neurologist is guided by the history, deliberately choosing those sites that the current clinical assessment indicates not to be involved. For example, for patients with recent onset of symptoms attributable to a spinal cord lesion, we scan the brain and in some instances select visual or auditory evoked potentials. In the context of recent visual loss, brain and possibly spinal MRI – on occasions supplemented by somatosensory and auditory evoked potentials – are appropriate methods for exploring clinically unaffected parts of the nervous system. There is a catch, however. Moving straight to the clinically unaffected nervous system on the assumption that the presenting syndrome is the result of inflammation and demyelination runs the risk of missing a local structural lesion. Therefore, in this example, the cord should also be targeted to exclude other diagnoses.

In cases where the diagnosis remains in real doubt, it is often helpful to answer two questions. First, is there evidence for the pathological process of demyelination? This can be inferred from the presence of a delayed evoked potential with a well-preserved waveform, though considerable caution is needed when this appears distorted (see Chapter 13). Since demyelination, axonal loss and gliosis each occur in multiple sclerosis, it might be hoped that imaging appearances would suggest the diagnosis, but no one morphological component has a specific imaging marker and these tissue-based interpretations cannot therefore reliably be made. Second, is there an abnormality of the immune mechanism in relation to the central nervous system? This is most readily judged from examination of the cerebrospinal fluid which will provide evidence for intrathecal synthesis of oligoclonal immunoglobulin G. This approach is particularly helpful in complex cases where considerable doubt remains about the disease mechanism, and in patients presenting with progressive syndromes attributable to a single site in which, over and above exclusion of a structural lesion, other disease

processes could be involved – motor neuron disease, hereditary spastic paraplegia or spino-cerebellar degeneration. In these and other situations, the issue is to get a lead on the underlying disease process despite the relative or complete absence of MRI abnormalities. Examination of the cerebrospinal fluid is also of considerable importance in the investigation of individuals where imaging is likely to be relatively uninformative, such as the older patient with longstanding and previously undiagnosed demyelinating disease or those with genuinely late onset disease, in whom the specificity of MRI white matter lesions is low. There are also occasions when MRI abnormalities are not apparent, or are of a minimal nature such that specific diagnostic criteria for multiple sclerosis are not fulfilled, yet where the presence of oligoclonal bands and delayed visual evoked potentials suggest demyelination, and one is reminded that MRI abnormalities are not required to make a clinical diagnosis of multiple sclerosis. Nevertheless, we do recommend especial caution in making the diagnosis when there are no abnormalities to be seen on good quality images obtained from both the brain and the whole of the spinal cord – such a finding must be very rare in clinically definite disease.

When the clinical picture is not episodic, or does not change while the patient is under observation, the demonstration of new focal lesions on MRI carried out over time may be very helpful in establishing the multiphasic nature of the disease process leading to the diagnosis of multiple sclerosis. Again, the most recent diagnostic criteria for multiple sclerosis allow for the criterion of dissemination in time to be fulfilled by MRI evidence alone (W.I. McDonald *et al* 2001).

In rare instances, the diagnosis of multiple sclerosis will be established by histopathological examination of a brain biopsy. The setting in which this usually occurs is a patient with an acute and fulminant presentation, clinical features indicating a rapidly progressing cerebral hemisphere lesion, and the radiological finding of a large mass lesion or lesions in the cerebral white matter. The suspicion of cerebral tumour or of an atypical inflammatory or infectious process leads to biopsy and correction of the diagnosis to inflammatory demyelination.

It is important again to stress that no one of the routinely used investigations (MRI, cerebrospinal fluid and evoked potentials) provides a result that is pathognomonic for multiple sclerosis. Formulation of the diagnosis depends on giving due weight to each element of the clinical and investigative picture. Herein lies the skill of the neurologist. Having outlined the general approach to the use of investigations, we now describe what they have to offer.

MAGNETIC RESONANCE IMAGING

It is difficult for the younger neurologist to appreciate the changes in practice arising from the introduction of brain imaging in the early 1970s. This has become an enormously important tool in clinical medicine, especially neurology. MRI provides noninvasive high-resolution and relatively artefact-free images of the brain and spinal cord and has the advantages over computed tomography (CT) scanning of not being subject to bone hardening influences, and proving uniquely sensitive in detecting many extrinsic and intrinsic pathological conditions. The value of MRI was recognized by the award of the Nobel Prize in Physiology or Medicine in 2003 to two pioneers of the technique for human imaging: Dr Paul Lauterbur and Sir Peter Mansfield (see Chapter 1; Gore 2003). In patients with spinal cord disease, the availability of MRI has rendered the earlier, invasive method of myelography obsolete. The opportunities for laboratory evaluation of multiple sclerosis were transformed with the introduction of MRI (I.R. Young *et al* 1981).

Methodology

MRI scanners are large magnets that produce a strong local magnetic field. This is created within the scanner by generating currents in coils surrounding the bore after they are cooled to an extremely low temperature using liquid helium (these are known as superconducting magnets). In body tissues, atoms that contain an uneven number of protons and neutrons have a small magnetic charge (such as ^{1}H, ^{23}Na, ^{31}P). When a subject is placed in the strong magnetic field, slightly more of these nuclei are oriented parallel rather than at an angle to the strong external field and, thus, they generate a net magnetization along the axis of this orientation. By applying radiofrequency pulses, the magnetization of the tissue can be excited to produce a nuclear magnetic resonance (NMR) signal that is detected by an external receiver. Using mathematical methods, such as two-dimensional Fourier transformation, together with additional gradient pulses that alter the local magnetic field in space, it is possible to locate all of the acquired NMR signals in their correct spatial positions, and thereby to produce two- or three-dimensional images.

The ^{1}H protons constitute by far the most abundant nuclei in the body from which NMR signals can be generated. Most protons in tissue are contained in water molecules (although fat protons also produce NMR signals at sites where they are concentrated such as the orbit). After the initial exciting radiofrequency pulse is discontinued, the water protons relax back to their resting state orientated along the strong magnetic field of the scanner. This process is governed by two main NMR properties – T_1 (longitudinal) and T_2 (transverse) relaxation. Thus MRI generates tissue contrast largely as a result of variations in the amount (proton density) of water and its T_1 and T_2 relaxation times. In turn, these are influenced by the macromolecular environment of the water molecules. Additional properties that can influence image contrast on certain MR sequences are diffusion of the protons and magnetization transfer (the latter is the transfer of magnetization between the protons when they exist in different physicochemical states).

Given that the dominant mechanism for differentiating normal and pathological tissues on conventional MRI is the concentration and macromolecular environment of water, it is possible to see that this brings a fundamental strength and weakness of the modality for diagnosis. The strength is a remarkably high sensitivity in detecting pathological abnormalities in soft tissue. The weakness is the limited pathological specificity. An important adjunct in diagnostic imaging is the use of paramagnetic gadolinium-containing chelates as contrast agents. Gadolinium contains seven unpaired electrons and water protons that come within its vicinity experience a marked decrease in their T_1 relaxation rate. Thus areas of contrast enhancement (increased signal) are seen on T_1-weighted scans. Gadolinium chelates do not enter the normal brain because of the tight blood–brain barrier but they will enter regions where this has been made permeable.

Clinically definite multiple sclerosis

It is important at the outset to reiterate that all images depend ultimately on the relative amounts and physicochemical environment of water protons in each area of the brain. The changes produced by disease may be characteristic but, by their nature, cannot be specific for any particular pathological process. It follows that the diagnosis of multiple sclerosis cannot be made on the basis of MRI alone. That said, the form and distribution of MRI abnormalities in multiple sclerosis are such that the appearances in any one case may be highly suggestive. MRI is accordingly of great value in clinical neurology and the assessment of individual patients. Its contribution, taken in the context of the remaining clinical and investigative picture, is often decisive.

Brain T_2-weighted MRI

T_2 contrast is the key feature that gives these approaches a high sensitivity for depicting focal white matter lesions in multiple sclerosis. This may be achieved using spin echo, fast spin echo or fast fluid attenuated inversion recovery (FLAIR) sequences. Multiple areas of high signal are seen in the periventricular region in 95% of patients. The abnormalities may be either discrete and focal (Figure 7.2) or confluent (Figure 7.3). They tend to involve the deep rather than the more peripheral white matter, although focal lesions are common enough in the periphery. The opposite distribution is more characteristic of vascular disease (Figure 7.4: see below), but neither is specific. Juxtacortical lesions (in subcortical white matter and abutting the cortex) are characteristic of multiple sclerosis, being present in about two-thirds of patients (D.H. Miller 1988; Figure 7.5). Conversely, sparing of the subcortical U-fibres is observed in some forms of arteriosclerotic small vessel disease. The rare involvement of the corpus callosum in vascular disease contrasts with the frequent location of lesions at this site in multiple sclerosis (Gean-Marton *et al* 1991; Offenbacher *et al* 1993). Corpus callosum lesions are a useful diagnostic feature best appreciated on sagittal T_2-weighted images, although they can also be observed on the more frequently acquired axial images (Figure 7.2). Lesions in the posterior visual pathways, most notably the optic radiations, are frequently seen (Hornabrook *et al* 1992; Figure 7.6).

Other common sites of involvement in multiple sclerosis are the brainstem and cerebellum (Barkhof *et al* 1997a; Figure 7.7). Brainstem lesions characteristically abut onto cerebrospinal fluid spaces, both anteriorly and adjacent to the fourth ventricle or aqueduct. In contrast, arteriosclerotic small vessel disease more often produces abnormalities in the central pons or midbrain that evidently do not extend to the parenchymal surface. Lesions of cerebellar white matter are seen in about 50% of patients with clinically definite multiple sclerosis.

Abnormalities of the grey matter, defined by MRI, occur much less often than those present in white matter. In our own series, the basal ganglia are affected in about 10% of cases (Miller *et al* 1997; Ormerod *et al* 1987). The low sensitivity of conventional MRI contrasts with the high frequency of pathological abnormality found in the thalamus post mortem (Cifelli

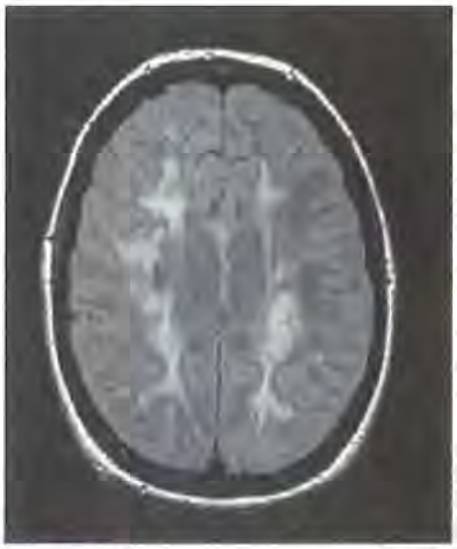


Figure 7.3 Multiple sclerosis. T_2-weighted axial brain MRI shows confluent periventricular abnormalities.

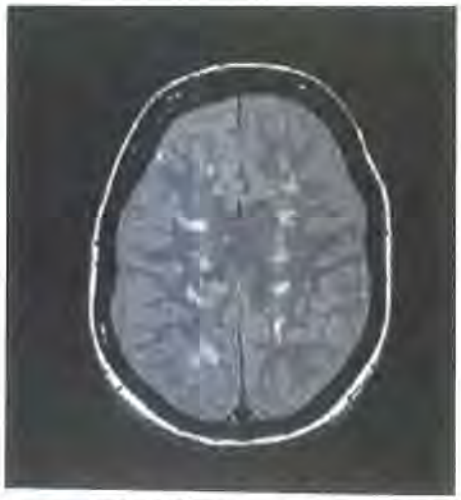


Figure 7.2 Multiple sclerosis. T_2-weighted axial brain MRI reveals multiple periventricular and discrete white matter lesions in addition to involvement of the corpus callosum.

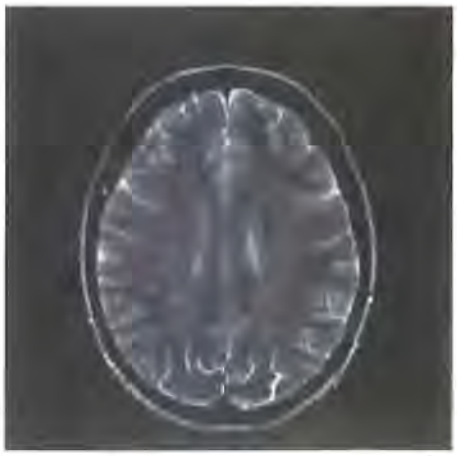


Figure 7.4 T_2-weighted MRI showing subcortical lesions that are characteristic – though not specific – for small vessel disease.

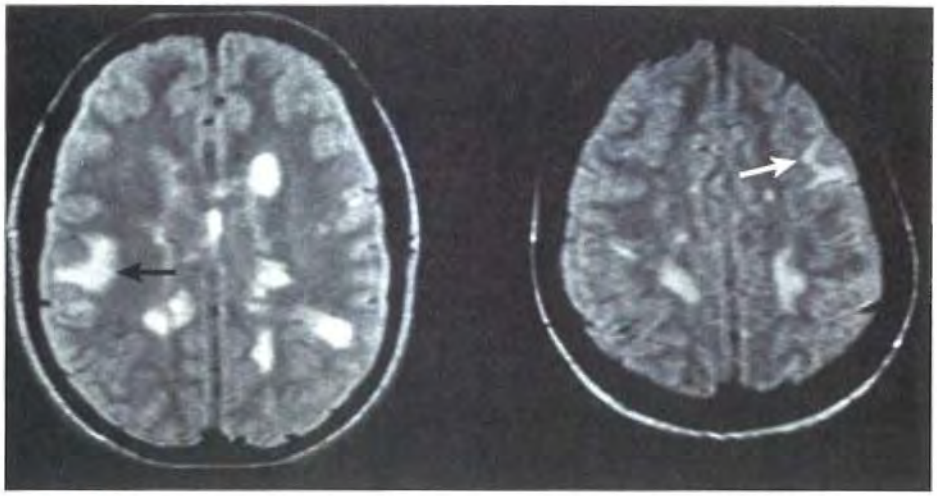


Figure 7.5 Multiple sclerosis. T_2-weighted MRI scans show juxtacortical lesions (arrowed).

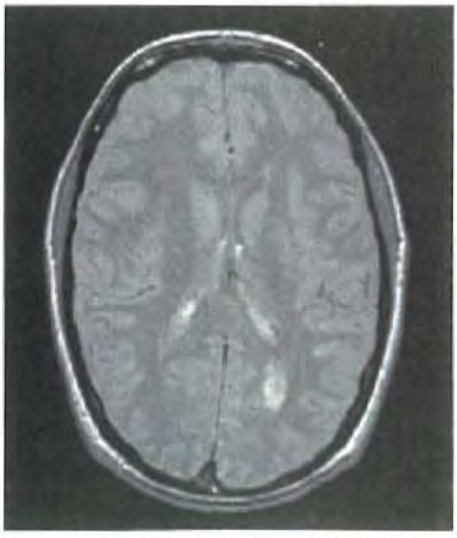


Figure 7.6 Multiple sclerosis. T_2-weighted MRI shows a lesion in the optic radiation.

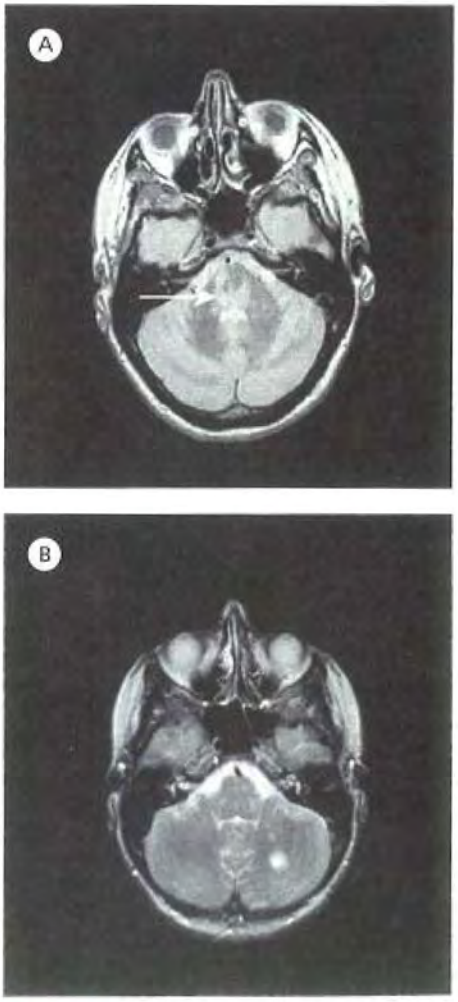


Figure 7.7 Multiple sclerosis. T_2-weighted MRI scans. (A) Lesion in the brainstem. (B) Lesion in the cerebellar white matter.

et al 2002). Cortical involvement, although commonly demonstrated at autopsy (Brownell and Hughes 1962; D. Kidd *et al* 1999a; Petersen *et al* 2001) is also infrequently recognized on routine scans. In part, this is because of partial volume effects but more likely reflects the fact that cortical plaques of demyelination have proton density and T_2 relaxation measures only marginally different from the surrounding grey matter. Cortical lesions are occasionally seen using gadolinium enhancement (see below). White matter lesions at the cortico-medullary junction are more readily seen using fast FLAIR sequences (Figure 7.8) and such lesions may on occasions extend into the cortical grey matter. The detection of intracortical lesions has been recently found to be improved by the use of a 3D double-inversion recovery sequence (Geurts *et al* 2005), although still only a minority of pathologically detected lesions is visible on MRI. Hypointensity on T_2-weighted images is reported in both cortical and deep grey matter structures in multiple sclerosis (Bakshi *et al* 2001; 2002; Grimaud *et al* 1995; Tjoa *et al* 2005) and has been associated with increasing disability, T_2 lesion load and brain atrophy. T_2 hypointensity may reflect increased iron deposition associated with neurodegeneration.

Although the great majority of brain lesions in multiple sclerosis are <5 mm in diameter, very large lesions occasionally occur and the extent of mass effect may even suggest the differential diagnosis of cerebral tumour (Figure 7.9). The detection of additional typical white matter lesions will give a clue to the correct diagnosis but, on occasion, uncertainty is such that biopsy is performed. A few large lesions exhibit multiple concentric rings of alternating high and low signal. This radiological appearance probably corresponds to the alternating bands of demyelination and myelination reported in Balo's concentric sclerosis (Iannucci *et al* 2000a; Stadelmann *et al* 2005; Figure 7.10). Acute lesions often display a single concentric ring of low signal on T_2-weighted images that correlates with macrophage infiltration and lipid breakdown at the lesion edge, and with gadolinium enhancement on post contrast T_1-weighted scans (see below).

Compared with T_2-weighted spin echo and fast spin echo sequences, the fast FLAIR sequence has the advantage of greater sensitivity in the cerebral hemispheres, especially subcortical white matter (Filippi *et al* 1996). This advantage is offset by it being less sensitive in the posterior fossa (Gawne-Cain *et al* 1997), and spinal cord (Stevenson *et al* 1997). Fast spin echo T_2-weighted sequences have largely replaced conventional spin echo sequences as they enable more rapid scanning of the brain and spinal cord. In the NMR Research Unit at Queen Square, London, the standard diagnostic T_2-weighted imaging sequence now is a double-echo proton-density and T_2-weighted fast spin echo, with which 3-mm axial contiguous slices and whole spinal cord 3-mm contiguous sagittal images can be captured in 6 and 10 minutes, respectively (Miller *et al* 1997). Many centres also add a fast FLAIR sequence because it makes cerebral white matter lesions more conspicuous. A gadolinium enhanced T_1-weighted sequence is also being increasingly used in the diagnostic workup (Fazekas *et al* 1999) and should now be used routinely in patients with single clinical episodes where it may contribute to the earlier diagnosis of multiple sclerosis (W.I. McDonald *et al* 2001).

Spinal cord T_2-weighted MRI

The spinal cord is commonly involved radiologically, whether or not this part of the central nervous system manifests symptoms and signs. Cord lesions are best detected on proton density and T_2-weighted images. In the sagittal plane, the lesions are usually less than one vertebral segment in length and occupy only part of the antero-posterior diameter of the cord (Figure 7.11). Axial scans reveal lesions involving only part of the cross-section of the cord, characteristically asymmetric and extending to the surface, sometimes in a wedge shape (Lycklama *et al* 2003; Figure 7.12). Although involvement of posterior and lateral quadrants is frequently seen, lesions not uncommonly extend into the central grey matter. Acute lesions may display swelling and those present over a period of time are associated with focal atrophy of the cord.

The sequences most often used to depict spinal cord lesions in multiple sclerosis are sagittal T_2-weighted fast or conventional spin echo (Figure 7.11), on occasions complemented by axial T_2-weighted imaging. The latter is useful in confirming an equivocal lesion seen on sagittal imaging. Short tau inversion recovery

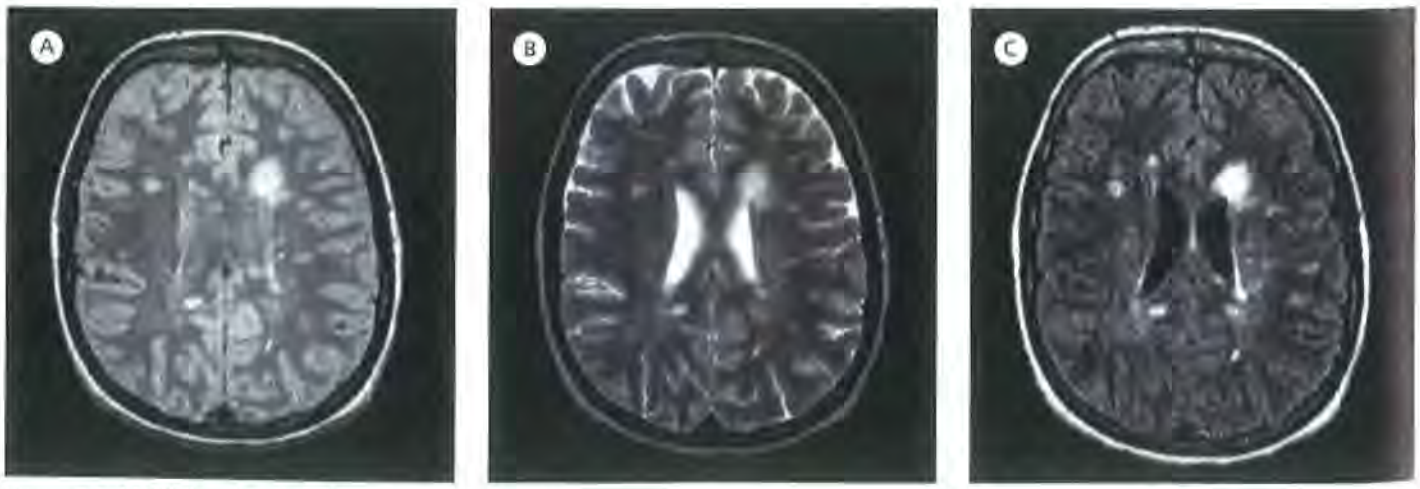


Figure 7.8 Multiple sclerosis lesions depicted using (A) proton density, (B) T_2-weighted, and (C) fast FLAIR sequence. Several subcortical lesions are better seen on fast FLAIR.

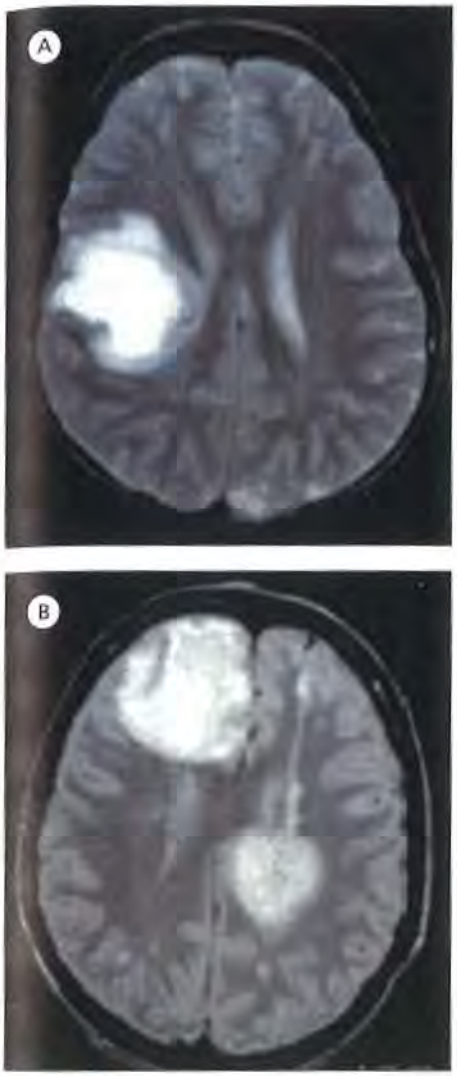


Figure 7.9 Multiple sclerosis. T_2-weighted scans showing large cerebral hemisphere lesions with mass effect. Kindly provided by Dr Claudia Lucchinetti.

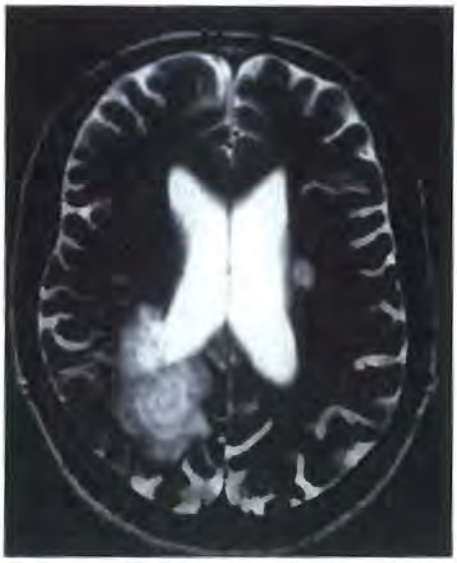


Figure 7.10 Multiple sclerosis. T_2-weighted MRI shows a lesion with alternating bands of high and normal signal (Balo's concentric sclerosis). From Kastrup *et al* (2002) with permission.

Figure 7.11 Multiple sclerosis. T_2-weighted sagittal MRI of the spinal cord shows multiple, small intrinsic lesions (arrowed).

fast spin echo (fast STIR) imaging has a slightly higher sensitivity than fast or conventional spin echo in detecting some cord lesions but this gain is offset by more frequent occurrence of artefacts (Bot *et al* 2000). Fast STIR has not become a part of the standard protocol for detecting spinal cord lesions.

Abnormalities in the cord may be seen when none are detectable in the brain, a finding of particular importance in primary progressive multiple sclerosis where cerebral lesions are less extensive than in other forms of the disease, and may even be absent (Kidd *et al* 1993). Thorpe *et al* (1996b) emphasized the value of cord imaging in 20 patients with clinically suspected multiple sclerosis but normal or near normal brain MRI. All 20 patients exhibited at least one focal cord lesion (median 2; range 1–6). The value of other laboratory investigation in such cases was also emphasized by the presence of cerebrospinal fluid oligoclonal bands in 13/15 and delayed visual evoked potentials in 10/18 subjects. Diffuse hyperintensity on proton density weighted images of the cord may also be seen, more so in primary progressive than in other forms of multiple sclerosis (Lycklama *et al* 1998).

As with the corpus callosum, the cord is rarely involved by vascular disease and, unlike the cerebrum, asymptomatic areas of high signal are very uncommon as an incidental finding with increasing age (Thorpe *et al* 1993). A recent study compared brain and spinal cord MRI in 25 patients with clinically definite

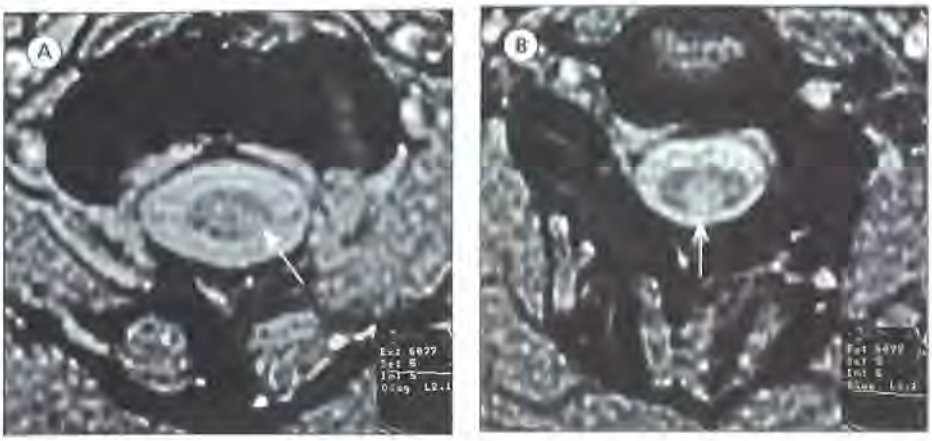


Figure 7.12 Multiple sclerosis. (A) and (B) T_2-weighted axial MRI scans through the spinal cord show two intrinsic lesions that involve only part of the cord cross-section and extend to the surface of the cord (arrows). Kindly provided by Dr Katherine Miszkiel.

multiple sclerosis and 66 with other neurological disorders, including inflammatory conditions (49 cases including systemic lupus erythematosus, Sjogren's syndrome and sarcoidosis) and cerebrovascular disease (17 cases; Bot *et al* 2002). In the brain, MRI revealed abnormalities in 100% of individuals with multiple sclerosis and in 56% of those with other diseases. In the cord, high signal lesions were seen in 92% with multiple sclerosis but only 6% with other diseases.

Gadolinium enhancement

An important step forward in the assessment of multiple sclerosis by MRI was the introduction of gadolinium-DTPA (diethylenetriamine pentacetic acid) and other gadolinium containing chelates as enhancing agents (R.I. Grossman *et al* 1986; Miller *et al* 1988b). Gadolinium-DTPA is normally excluded from the parenchyma of the brain and spinal cord by the blood–brain barrier and so the presence of enhancement indicates an increase in vascular permeability that, in the context of multiple sclerosis and related disorders, occurs in association with inflammation. The standard method for detecting enhancement is to perform a T_1-weighted scan 5–10 minutes after a bolus intravenous injection of 0.1 mmol/kg of a gadolinium-containing contrast agent. Various appearances are encountered in enhancing lesions (Figure 7.13). Some lesions tend to enhance uniformly, and focal homogeneous enhancement may be seen within larger lesions. Other, often larger, lesions show ring enhancement, corresponding with the pattern of inflammation sometimes seen at post mortem. The rings may be complete or partial – the latter, also called an incomplete ring, considered as particularly characteristic for multiple sclerosis (Masdeu *et al* 2000). However, ring enhancement is seen in a number of other pathological conditions, including brain abscess and metastases.

Enhancement is the earliest change detectable by MRI in the development of most new lesions in relapsing–remitting and secondary progressive multiple sclerosis (Figure 7.14; Kermode *et al* 1990; see Chapter 12). Enhancement is almost invariably seen in the relevant pathway at the onset of symptoms. It is also more commonly seen at other sites during clinical relapse (R.I. Grossman *et al* 1986; Kappos *et al* 1999; Smith *et al* 1993) more so than during remission. These sites include the cerebral cortex where, for the reasons given above, unenhanced lesions are difficult to visualize. However, most enhancing lesions occur in cerebral white matter and are as abundant in the subcortical and juxtacortical regions as in deep white matter (M.A. Lee *et al* 1999; Figure 7.13). It is not uncommon to see several areas of enhancement in the white matter at a particular time. Rarely, >100 such areas may be visible (Figure 7.15).

Enhancement lasts on average 4–6 weeks (Figure 7.13; Miller *et al* 1988b). It may, however, disappear more rapidly and in studies of patients undergoing weekly MRI, some new lesions enhance for as little as 1 week (Cotton *et al* 2003; H.M. Lai *et al* 1996). The fact that enhancement rarely lasts more than 2–3 months could be useful in helping to distinguish multiple sclerosis from other conditions such as tumour or neurosarcoidosis, where enhancement (without corticosteroids or other treatment) can be expected to persist. A further helpful feature is the extensive meningeal enhancement often seen in neurosarcoidosis but not as a feature of multiple sclerosis (see Figure 8.19; Lexa and Grossman 1994).

The high frequency of gadolinium enhancement in new lesions is seen in the relapsing–remitting and secondary progressive phases of the disease. However, there is convincing evidence that enhancement is less frequent in those patients with secondary progressive disease in whom superimposed relapses are no longer occurring (Kidd *et al* 1996; Tubridy *et al* 1998b). It is very strikingly more rare in primary progressive disease, in which only about 5% of new lesions enhance (A.J. Thompson *et al* 1991). The implications of this observation for understanding of the pathogenesis are discussed in Chapter 13.

There is evidence to suggest that some lesions which fail to show enhancement using conventional doses of gadolinium, standard sequences and imaging up to 20 minutes after bolus injection, may nevertheless have abnormal vascular permeability (Barnes *et al* 1991; Filippi *et al* 1995b; Silver *et al* 1997). The number of visible lesions may increase by 120% when a triple dose of a gadolinium chelate (0.3 mmol/kg) is combined with magnetization transfer imaging and the scan is delayed for 40–60 minutes after injection. The most important single factor contributing to the increase in sensitivity is the higher dose of contrast. Most additional enhancing lesions are seen in patients who already have some other enhancing lesions using single dose contrast. These methods to increase sensitivity are not relevant diagnostically but may have advantages in clinical trials by reducing the size of the required sample population (Koudriavtseva *et al* 1997; D.H. Miller *et al* 1996; Silver *et al* 1997; 2001). However, even in that context, the gains are

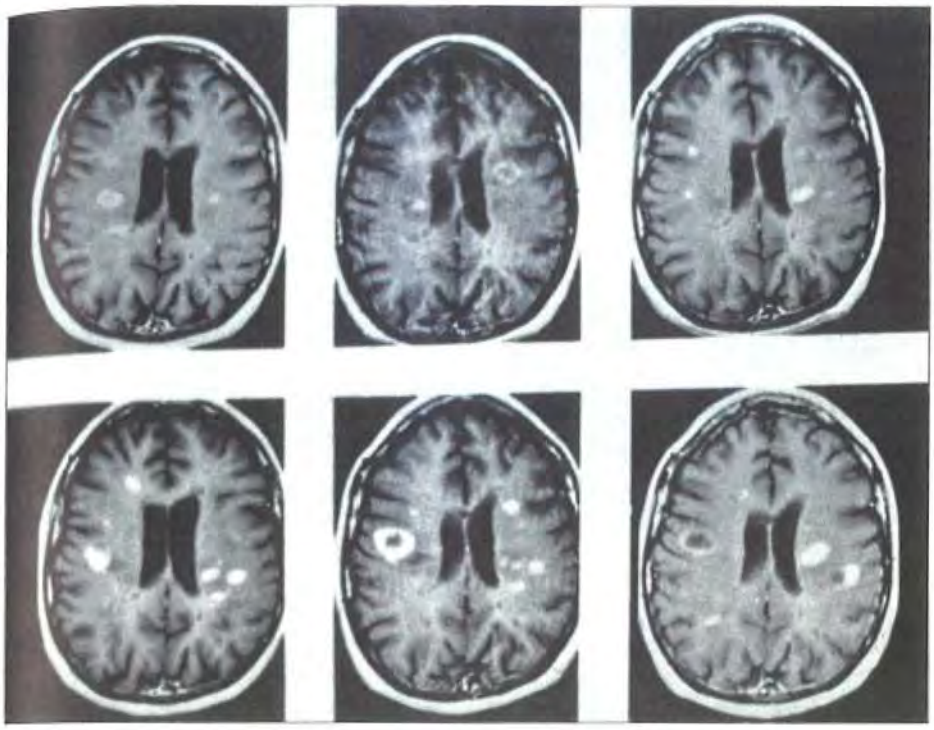


Figure 7.13 Serial monthly gadolinium enhanced T_1-weighted brain MRI over 6 months (starting at the top left and ending at the bottom right) in a patient with relapsing–remitting multiple sclerosis. Several new enhancing lesions appear each month and cease enhancing 1 or 2 months later. Some lesions show homogeneous enhancement while others display ring enhancement.

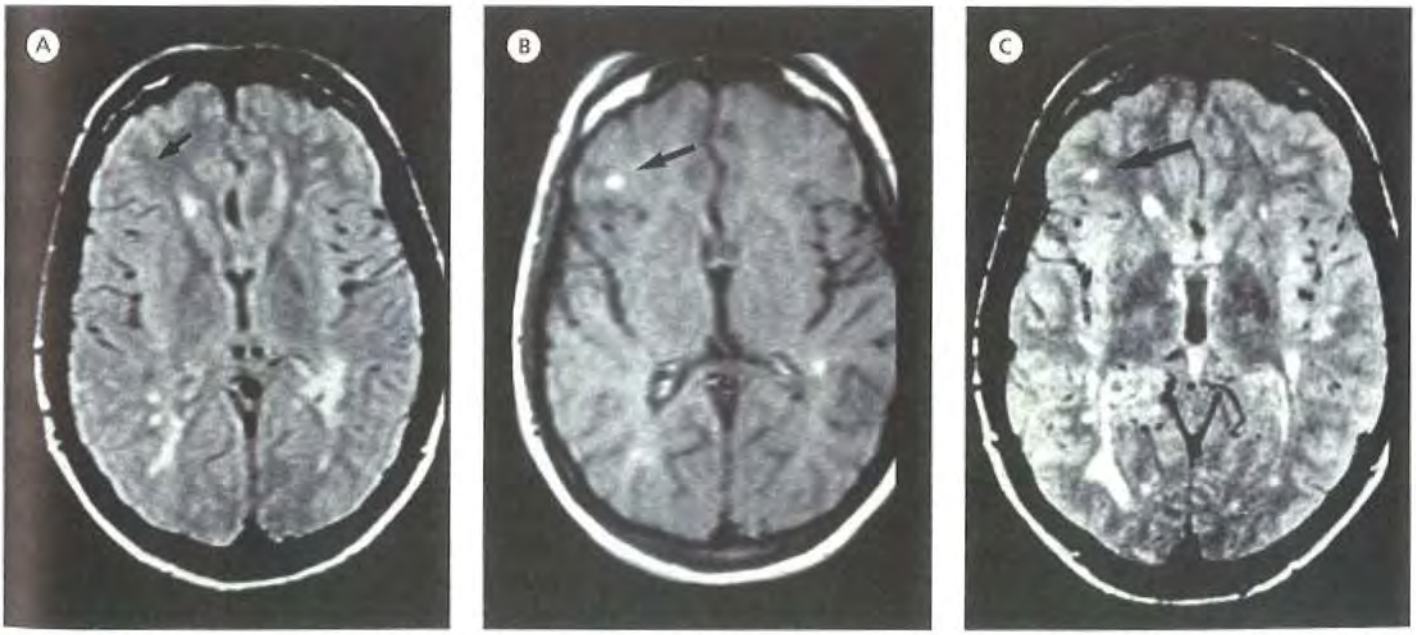


Figure 7.14 (A) T_2-weighted image showing multiple lesions in clinically definite multiple sclerosis; note that no abnormality is visible at the tip of the arrow. (B) Gadolinium-enhanced T_1-weighted image. Note that there are several areas of enhancement, one of which is at the tip of the arrow. This image was taken a matter of minutes following the T_2-weighted images. (C) T_2-weighted image some weeks later, now showing a lesion visible at the tip of the arrow.

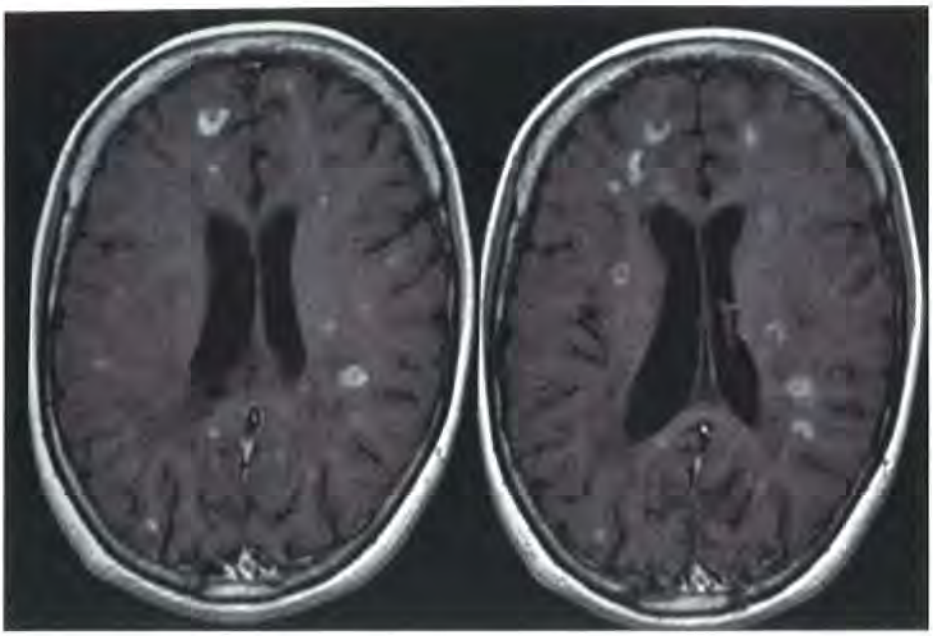


Figure 7.15 Gadolinium enhanced T_1-weighted MRI in clinically definite multiple sclerosis. This patient has >100 enhancing lesions at this time.

modest because the increase in overall sensitivity is offset by a greater variability in activity between patients. There is some evidence that the frequency of gadolinium enhancing lesions is highest in the earliest years of the disease, and may even occur early in primary progressive disease when triple dose gadolinium is used. In a recent study of 45 patients with primary progressive multiple sclerosis and disease duration <5 years, >40% had enhancing lesions (Ingle *et al* 2005).

T_1 hypointense lesions

Even though sequences providing proton density and T_2-weighted images are now standard, T_1-weighted inversion recovery images were used first in the assessment of multiple sclerosis (I.R. Young *et al* 1981). However, the overall sensitivity of inversion recovery was subsequently shown to be less than for T_2-weighted MRI. More recently, there has been interest in the appearance of lesions seen on T_1-weighted spin echo images because of their potential for revealing evidence of parenchymal destruction (Van Waesberghe *et al* 1999). Whereas about 20–30% of chronic T_2 lesions are persistently T_1 hypointense on T_1-weighted spin echo sequences in multiple sclerosis (Figure 7.16), such an appearance is less common in the white matter lesions associated with normal aging and small vessel disease (Uhlenbrock and Sehlen 1989). Chronic T_1 hypointense lesions have been correlated with greater axonal loss than T_1 isointense lesions. However, T_1 hypointensity on a single scan that does not allow the age of lesions to be determined should be interpreted with some caution, because T_1 hypointensity is not uncommonly a reversible finding of acute gadolinium enhancing lesions (Bagnato *et al* 2003). Resolution of T_1 hypointensity, when it occurs in such lesions, takes place over several months.

Relationship of abnormal signal to pathology

With the advent of MRI, close similarity between the distribution of areas showing abnormal signal on MRI and the dis-

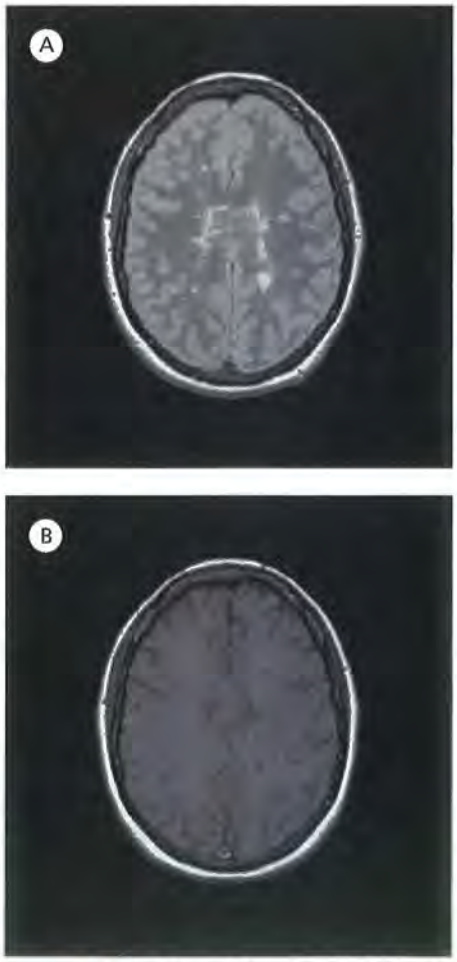


Figure 7.16 (A) T_2-weighted and (B) T_1-weighted MRI in multiple sclerosis. A minority of the T_2 lesions are visible as areas of T_1 hypointensity (colloquially called 'black holes').

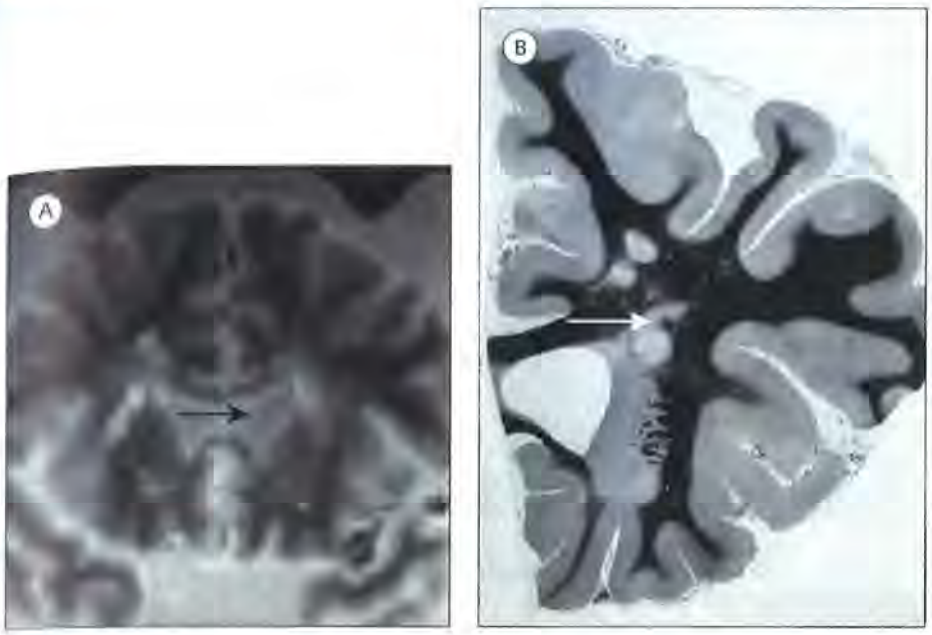


Figure 7.17 (A) T_2-weighted image of a formalin-fixed brain from a patient with clinically definite multiple sclerosis. (B) Section of the right hemisphere of the brain in a plane corresponding with the MRI in (A). There is good correspondence between the location of the imaging abnormalities and areas of demyelination (Heidenhein stain). From Ormerod *et al* (1987) with permission.

tribution of lesions at post mortem (see Chapter 12) soon suggested that the former represent plaques. This was more formally demonstrated by scanning formalin-fixed brain and correlating the images with tissue sections subsequently cut in the imaging planes (Figure 7.17; Ormerod *et al* 1987; W.A. Stewart *et al* 1986). More recent studies have indicated that not all MRI visible lesions correspond to classical plaques of demyelination. In some areas, inflammatory changes, such as microglial activation only, have been observed (De Groot *et al* 2001). Other T_2 lesions may represent areas of remyelination or shadow plaques (Barkhof *et al* 2003a). As described in Chapter 13, it has become clear that there is more to the interpretation of images than their topography, however important these correlations between imaging and pathology are.

In the early MRI literature, it was frequently reported that lesions could sometimes completely disappear, but this phenomenon is rarely seen with modern high-resolution scanners (A.J. Thompson *et al* 1991). Nonetheless, new lesions are seen to wax and wane in size over a matter of weeks (C. Isaac *et al* 1988; Willoughby *et al* 1989), and quantitative studies have shown, as expected, that at least some of the disappearing element of the lesions depicted on T_2-weighted or proton density images is attributable to oedema (Larsson *et al* 1988).

We now know that the residual abnormal signal in lesions originates from alterations in the amount and physicochemical state of extra- and intracellular water in the chronic plaques (Barnes *et al* 1988). Standard T_2-weighted MRI does not reveal either normal or pathological myelin and the common practice of referring to regions of abnormal signal as areas of demyelination is plainly wrong, and may even be misleading. Nor does it distinguish the extent of axonal loss in longstanding lesions.

Measures of atrophy

Another finding is the presence of apparently global spinal cord and cerebral atrophy, which may progress over as short a period as 12–18 months (Figure 7.18). It is seen at all stages of multiple sclerosis and becomes increasingly marked with clinical progression and increasing disability (Figure 7.19; Losseff *et al* 1996a; 1996b; D.H. Miller *et al* 2002). Recent studies have used statistical parametric mapping to segment white and grey matter, indicating that significant atrophy occurs in both types of tissue (Chard *et al* 2002a; Sastre-Garriga *et al* 2005). Grey matter atrophy involves both neocortex (DeStefano 2003) and deep grey matter (Cifelli *et al* 2002). About 45% of normal white matter consists of axons and it is likely that progressive atrophy reflects underlying neuroaxonal loss. Because it correlates with clinical disability, the measurement of spinal cord and brain atrophy holds promise as a method for the assessment of therapeutic efficacy in clinical trials (D.H. Miller *et al* 2002). Progressive grey matter atrophy and ventricular enlargement have been detected during the first 3 years of multiple sclerosis following presentation with a clinically isolated syndrome (Figure 7.20; Dalton *et al* 2004a). Progressive grey matter atrophy also occurs in the early years of both relapsing–remitting and primary progressive multiple sclerosis (Tiberio *et al* 2005; Sastre-Garriga *et al* 2005). It follows that a high priority for therapeutic research in multiple sclerosis should be to find treatments that prevent neuroaxonal loss in the early stages of the disease. Although atrophy can readily be appreciated by visual inspection of scans when severe, more subtle degrees can only reliably be measured using quantitative methods. It is important to note that since atrophy is a feature of many other neurodegenerative disorders, it is not a useful diagnostic feature in everyday clinical practice.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy is making a significant contribution to our understanding of the pathogenesis of multiple sclerosis (see Chapter 13) but it has not established a place in routine diagnostic practice. Instead of studying water protons, spectroscopy investigates other proton-containing metabolites. Two metabolites of particular interest are *N*-acetyl aspartate and

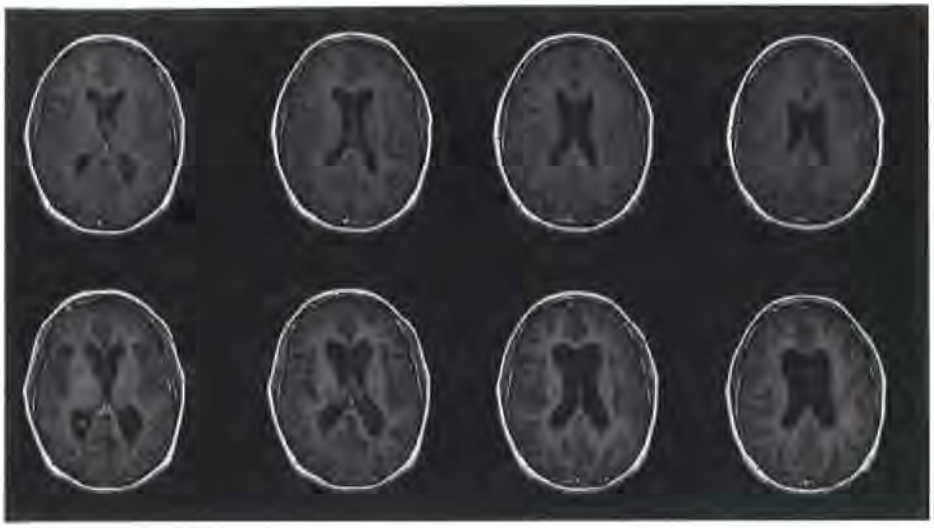


Figure 7.18 Serial T_1-weighted MRI over 18 months in a patient with secondary progressive multiple sclerosis showing striking development of atrophy. The top row shows baseline scans at four different levels in the brain and the bottom row shows the scans 18 months later at the corresponding levels.

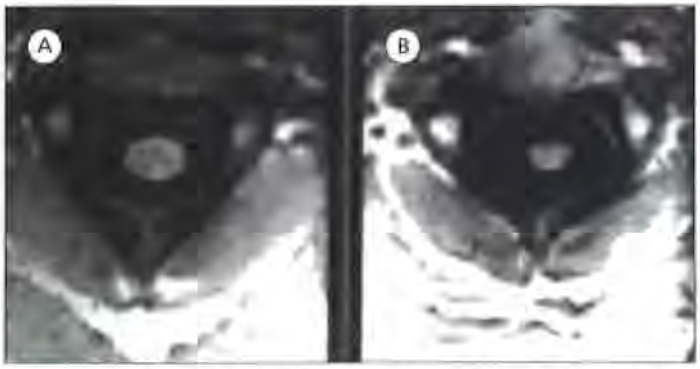


Figure 7.19 (A) Axial T_1-weighted through the upper cervical cord showing a normally sized cord in a multiple sclerosis patient with minimal disability (EDSS = 1). (B) Marked cord atrophy in another patient with severe disability (EDSS = 8). From Losseff *et al* (1996b) with permission.

myoinositol (Ins). *N*-Acetyl aspartate is contained almost entirely in neurons and axons, thus providing an indication of neuroaxonal damage and loss, which is thought to be the main substrate of irreversible disability in multiple sclerosis (Davie *et al* 1995; Fu *et al* 1998; Sarchielli *et al* 1999). However, decreases in *N*-acetyl aspartate are sometimes partly reversible (DeStefano *et al* 1997; Narayanan *et al* 2001). Reduction in *N*-acetyl aspartate sometimes reflects reversible mitochondrial dysfunction rather than cell death (R.E. Brenner *et al* 1993). Myoinositol is produced by glial cells. It is elevated in normal-appearing white matter early in multiple sclerosis, perhaps reflecting inflammation extending beyond focal lesions (Chard *et al* 2002b). There are several reasons why spectroscopy has a limited role in routine investigation and in resolving aspects of the differential diagnosis in multiple sclerosis. It is difficult to obtain reproducible spectra; the low signal to noise ratio of the metabolites limits the investigation to large lesions or normal appearing tissues; and broadly similar metabolic changes are seen in a number of different types of lesion. Reduced *N*-acetyl aspartate and increased choline-containing compounds are seen in tumours and leucodystrophies as well as demyelinating multiple sclerosis lesions, the former indicating axonal damage and the latter an increase in membrane turnover. One case has suggested that the lesions of acute disseminated encephalomyelitis may differ from multiple sclerosis and leucodystrophies in having a normal choline content (Bizzi *et al* 2001).

Magnetization transfer imaging

Magnetization transfer imaging is sensitive to tissue disorganization (Dousset *et al* 1992; 1994; 1995; Grossman 1994). An additional pulse is applied that interrupts the normal exchange of magnetization between freely mobile water protons and those bound to macromolecules, in particular myelin in normal-appearing white matter. Quantitative data from these various sequences are being evaluated and studies to date suggest that, compared with standard T_2-weighted lesion measures, they provide a closer reflection of disease progression and disability. The magnetization transfer ratio provides a sensitive measure of disease progression in normal-appearing white and grey matter (Filippi *et al* 1999a) and reveals abnormalities from the early stages of disease (Figure 7.21; G.R. Davies *et al* 2004; Traboulsee *et al* 2003). The lesion magnetization transfer ratio provides an indication of myelination (Barkhof *et al* 2003a; Schmierer *et al* 2004).

The magnetization transfer ratio has not proved to be of much value in differential diagnosis. Multiple sclerosis white matter lesions have been shown to have lower ratios than those caused by vascular disease or oedema (Gass *et al* 1994; Reidel *et al* 2003; Rovaris *et al* 2000b). Abnormalities have been detected in the normal-appearing brain tissue in multiple sclerosis but not in acute disseminated encephalomyelitis (Inglese *et al* 2002a). However, there is overlap between disease groups and controls. Lack of specificity, together with the difficulties of accurate quantification, have prevented the magnetization transfer ratio being used as a reliable and practical diagnostic tool for individual patients.

Functional MRI

Functional MRI (fMRI) investigates regional blood flow changes within the brain in response to specific activation algorithms. A more detailed account of the physiological principles of fMRI

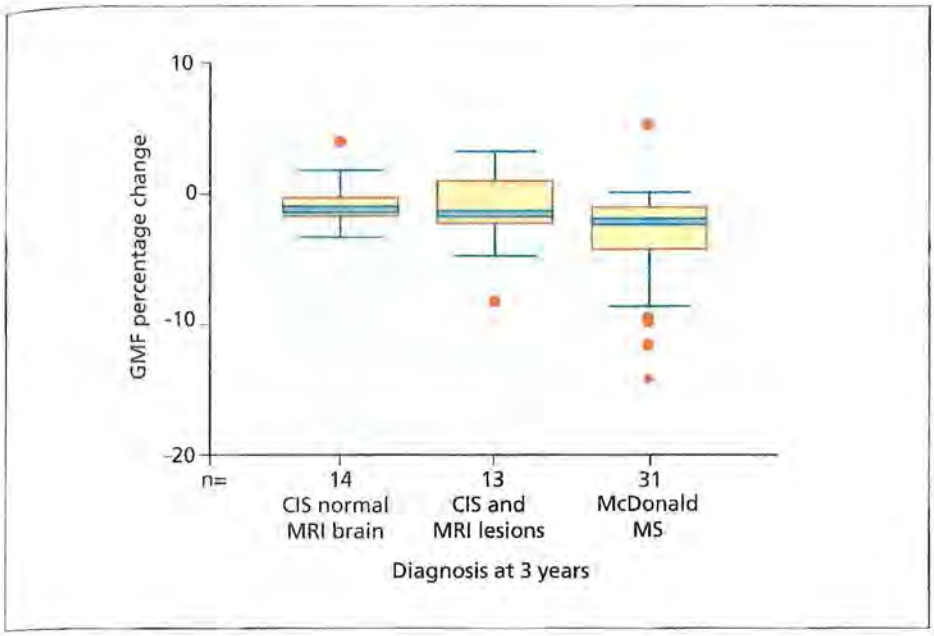


Figure 7.20 Box plot showing the medians, interquartile ranges (box), highest and lowest values (whiskers), excluding outliers (circles) and extreme value (asterisk) for grey matter fraction (GMF) percentage change in clinically isolated syndrome patients divided into those with (n = 13) and without (n = 14) MRI lesions, and individuals who developed multiple sclerosis within 3 years (n = 31). Significant grey matter atrophy was seen in those with a diagnosis of multiple sclerosis. Adapted from Dalton *et al* (2004a).

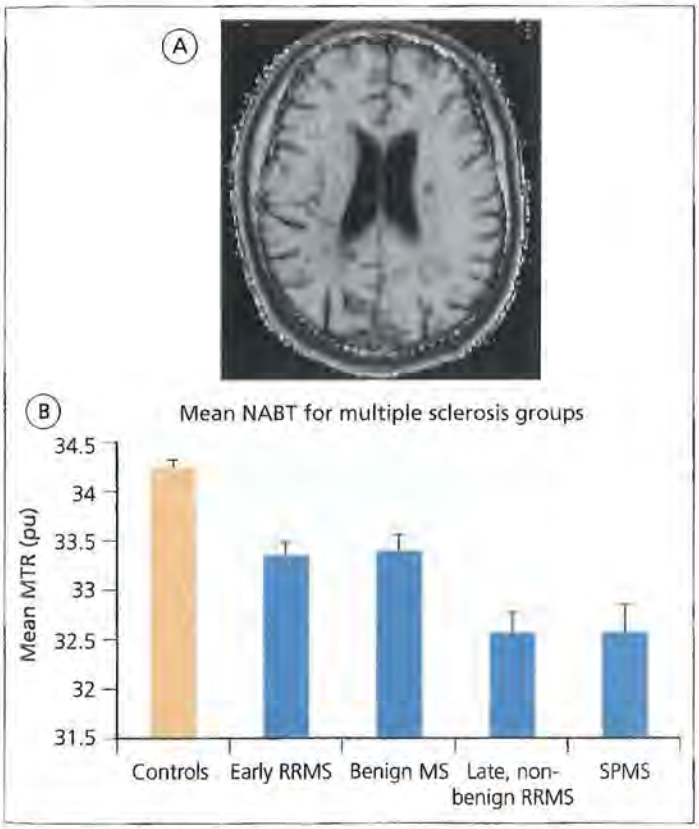


Figure 7.21 (A) Magnetization transfer ratio image of the brain. (B) Mean magnetization transfer ratio derived from histogram analysis of the normal-appearing brain tissue shows abnormalities in all multiple sclerosis clinical subgroups compared with controls, even those with relapsing–remitting disease (RRMS) and <3 years' disease duration. NABT = normal appearing brain tissue; SPMS = secondary progressive multiple sclerosis. From Traboulsee *et al* (2003) with permission.

and pathophysiological insights obtained in multiple sclerosis are provided in Chapter 13. Recent studies have shown that abnormal patterns of cerebral activation are already seen in patients with clinically isolated syndromes (Filippi *et al* 2004; Rocca *et al* 2005) A group of seven patients who had experienced a single episode of optic neuritis exhibited an abnormal and extensive pattern of activation beyond the primary visual cortex in response to a flashing light stimulus administered several years after the clinical episode (Figure 7.22; Werring *et al* 2000b). Another group of 16 patients with a variety of clinically isolated syndromes was reported to exhibit abnormal activation extending beyond the contralateral primary somatomotor cortex in response to a finger flexion extension algorithm, this occurring in spite of an absence of clinical motor dysfunction (Rocca *et al* 2003b). These studies indicate that cortical plasticity is a remarkably early feature in patients with central nervous system demyelination, and one must ask whether such altered and potentially adaptive activation patterns will have a prognostic or even diagnostic role. It seems unlikely that a major role will emerge for diagnosis, since the latter necessarily depends on showing dissemination in space and time of the underlying pathological (that is, structural) process *per se*, although it is intriguing that, in a recent small cohort study of 16 clinically isolated syndrome patients, early diagnosis of multiple sclerosis was more likely to follow in patients who exhibited a widespread and bilateral activation pattern to a unilateral upper limb motor activation paradigm (Rocca *et al* 2005).

Other methods

A number of quantitative MR measures have been used to investigate lesions and normal-appearing tissues. Diffusion weighted imaging has shown increased diffusion in normal-appearing white and grey matter (Cercignani *et al* 2001a; 2000b) and

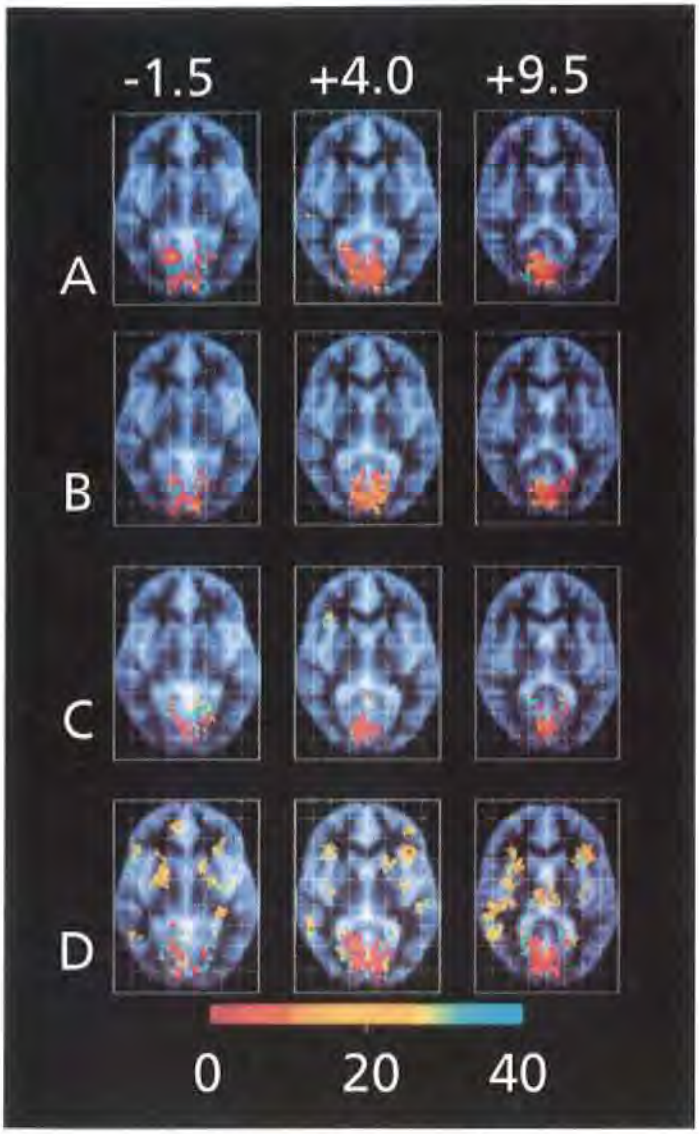


Figure 7.22 Functional MRI elicited response from monocular visual stimulation in healthy controls. (A) Left eye, (B) right eye, (C) patients with previous unilateral optic neuritis when stimulating the clinically unaffected eye and (D) affected eye. In healthy individuals, activation is largely confined to the primary visual cortex. Extrastriate activation is most apparent after stimulating the affected eye of patients. From Werring *et al* (2000b) with permission.

decrease in fractional anisotropy in white matter tracts (Ciccarelli *et al* 2001). Anisotropy is high in normal white matter tracts because diffusion is much higher along than across fibres. Thus, a decrease in anisotropy implies structural damage in the fibre pathway. Diffusion tractography is a promising tool for measuring fibre tract integrity by an assessment of their volume and fractional anisotropy (Ciccarelli *et al* 2003a; 2003b), although at present the measures have limited reproducibility and are confined to only the largest cerebral tracts (such as the optic radiation; Figure 7.23). Increased T_1-weighted relaxation has been shown in normal-appearing grey and white matter (C.M. Griffin *et al* 2002a). Perfusion is reduced in grey matter in progressive forms of multiple sclerosis (Figure 7.24) but is increased in white matter in relapsing–remitting disease (Rashid *et al* 2004). It is also increased for several weeks in white matter with normal appearance prior to a lesion appearing in relapsing–remitting disease (Wuerfel *et al* 2004). The increases in perfusion in these studies may reflect altered metabolic activity of the tissues as a result of inflammation during the relapsing–remitting phase. Such techniques offer valuable new windows for exploring and elucidating pathogenic mechanisms, and especially for understanding the nature of abnormalities beyond visible white matter lesions, but they do not currently have diagnostic utility.

A new area of MRI research and development revolves around efforts to achieve cellular and molecular specificity. The field is still at an early stage. MR contrast agents that use ultrasmall particles of iron oxide will produce a marked shortening of T_2 and T_1 relaxation times in regions where they accumulate, because of the creation of marked inhomogeneity of the local magnetic field. Such particles are avidly taken up by reticuloendothelial cells, and in monocytes and macrophages. In a study of 10 patients with multiple sclerosis in whom ultrasmall particles of iron oxide were injected intravenously, enhancement was seen in 33 lesions in nine patients on T_1 and T_2-weighted images (Dousset *et al* 2000). All but two of the 33 iron oxide (Sinerem) enhancing lesions also exhibited gadolinium enhancement, indicating the acute inflammatory nature of the lesions with breakdown of the blood–brain barrier. Gadolinium enhancing lesions are reported to contain activated macrophages (Brück *et al* 1997; D. Katz *et al* 1993) and collateral investigation in experimental autoimmune encephalomyelitis has shown good correspondence between areas of Sinerem enhancement and macrophage infiltration (Dousset *et al* 1999). The clinical study also revealed 24 additional lesions that displayed gadolinium but not Sinerem

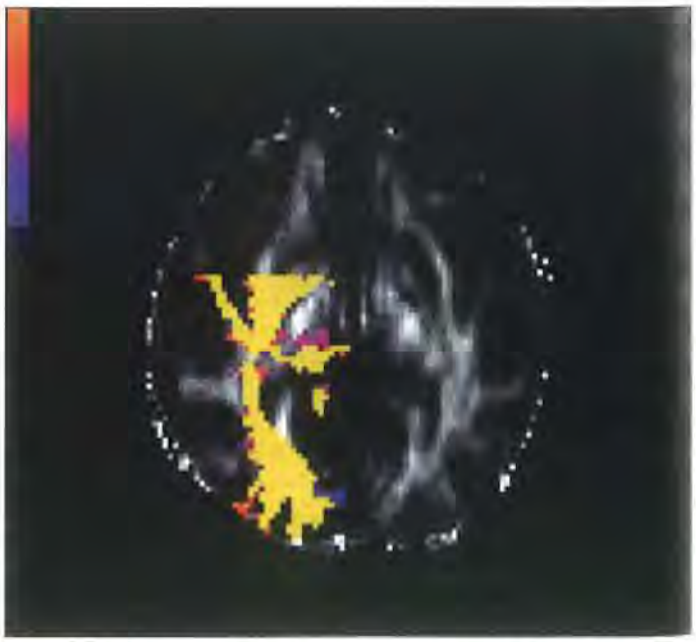


Figure 7.23 Diffusion tractography map generated from diffusion tensor MRI showing the optic radiation (indicated in yellow). Kindly provided by Dr Olga Ciccarelli.

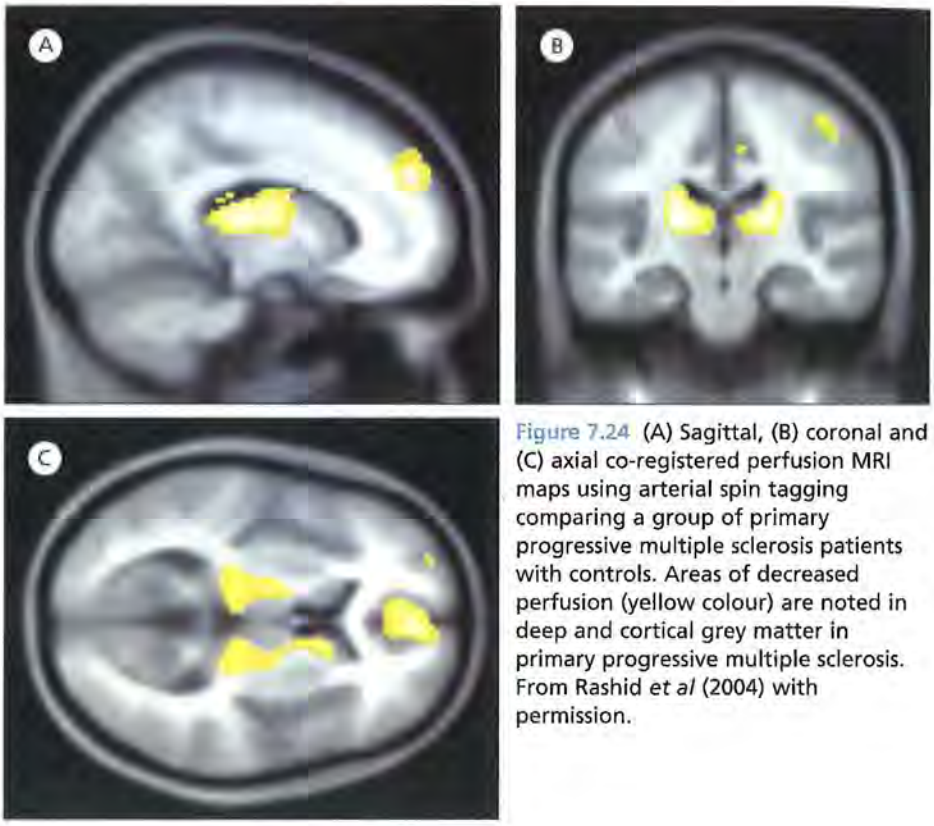


Figure 7.24 (A) Sagittal, (B) coronal and (C) axial co-registered perfusion MRI maps using arterial spin tagging comparing a group of primary progressive multiple sclerosis patients with controls. Areas of decreased perfusion (yellow colour) are noted in deep and cortical grey matter in primary progressive multiple sclerosis. From Rashid *et al* (2004) with permission.

enhancement. Obvious questions arise as to whether the presence of lesions displaying Sinerem enhancement is associated with greater tissue damage because of the presence of activated macrophages or a poorer clinical prognosis. Further studies that investigate such issues are awaited. Other targets for cell-specific MRI in central nervous system inflammatory/demyelinating diseases are T lymphocytes (S.A. Anderson *et al* 2004), and oligodendrocyte progenitors and stem cells (Frank *et al* 2003). Such approaches are currently experimental but have potential for translation to clinical studies with further research and development.

Other imaging and radiological techniques

As technologies available for depicting structure and function in the central nervous system became ever more sophisticated over the last 30 years, their potential application in the context of multiple sclerosis has been evaluated. Although MRI provides the main advance of clinical utility in relation to multiple sclerosis, there follows a brief review of the contributions from other modalities that have been used to image the nervous system in multiple sclerosis.

Computed tomography

Prior to the advent of MRI, CT scanning was sometimes used to demonstrate cerebral hemisphere lesions in multiple sclerosis, visible as multifocal areas of low attenuation in the white matter (Cala and Mastaglia 1976). Active lesions were also depicted as areas of high attenuation after the injection of iodinated contrast media (Vinuela *et al* 1982), but this was of limited value and the sensitivity of CT scanning was always poor. In the first comparative study of CT versus inversion recovery T_1-weighted MRI in 10 patients with multiple sclerosis, 19 lesions were detected on CT and 131 on MRI (I.R. Young *et al* 1981). The discrepancy in sensitivity between CT and MRI became even more apparent when T_2-weighted imaging was shown to be superior to inversion recovery for detecting multiple sclerosis lesions. High-resolution orbital CT is still useful for investigating patients presenting with undiagnosed optic neuropathies in whom the differential diagnosis may arise between optic neuritis, other inflammatory optic neuropathies or optic nerve compression.

Positron emission tomography (PET)

This modality has been used as a research tool to study multiple sclerosis. Decreased oxygen utilization has been observed in the brain (Brooks *et al* 1984), consistent with loss of neuroaxonal tissue. Another PET study, that used ^{18}F-deoxyglucose to quantify the cortical cerebral metabolic rate of glucose, reported reductions in the cortical and deep grey matter of multiple sclerosis subjects compared with healthy controls (Blinkenberg *et al* 2000). The decrease in glucose metabolism correlated with increasing T_2 lesion load and cognitive impairment. Single positron emission computed tomography (SPECT) studies have also revealed a correlation between decreased regional cerebral blood flow and cognitive impairment (Pozzilli *et al* 1991; Lycke *et al* 1993).

A PET radioligand marker (called PK11195) for peripheral benzodiazepine receptors, which are located on activated

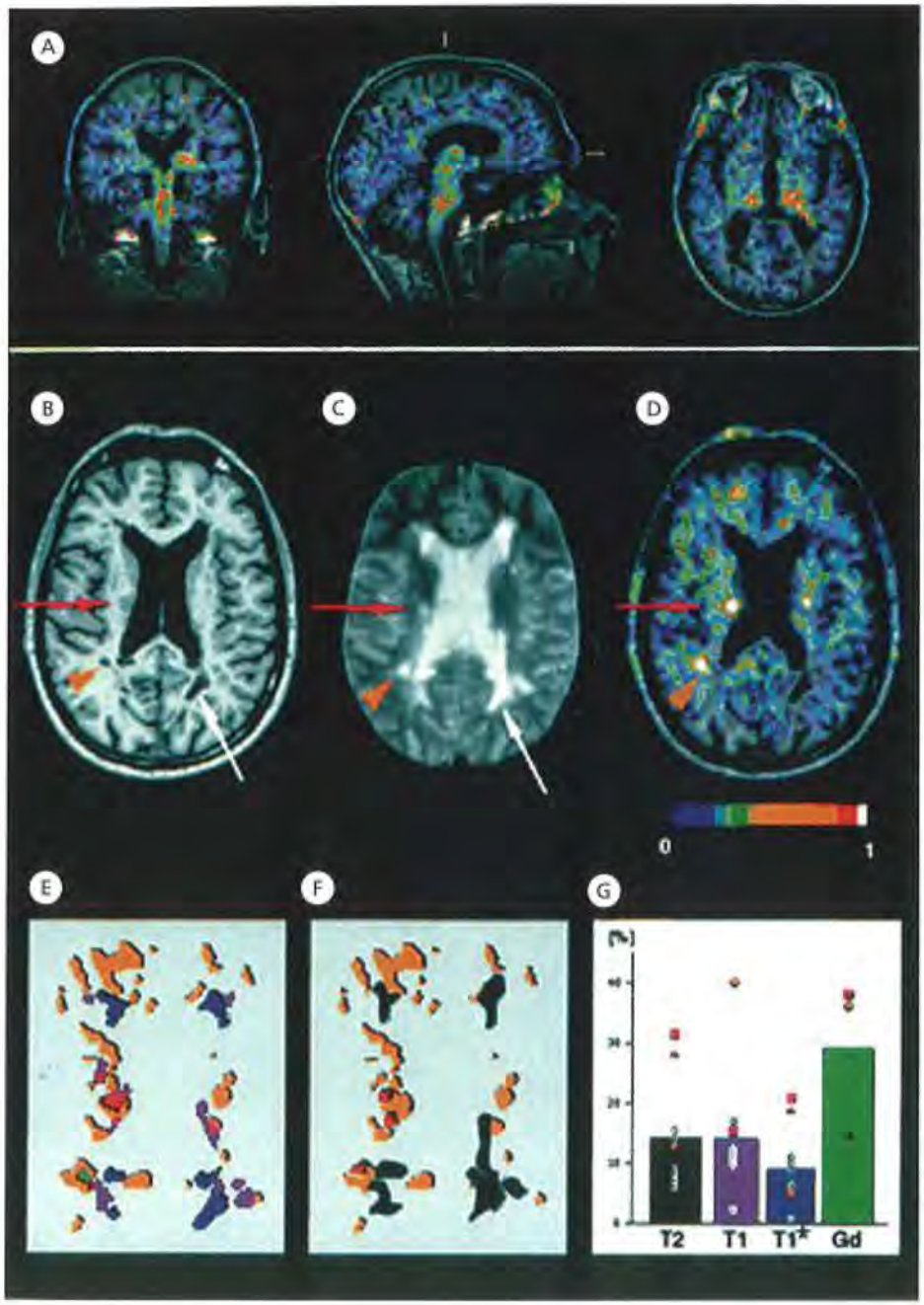


Figure 7.25 MRI and [^{11}C](*R*)-PK11195 PET. All images follow the radiological convention, i.e. the left side of the image corresponds to subject's right side. (A) Three orthogonal views of [^{11}C](*R*)-PK11195 images co-registered and overlaid on the MRI of Patient 9, showing spinothalamic tract-associated [^{11}C](*R*)-PK11195 signals extending through the brainstem and pons into the thalamus. (B–D) T_1-weighted (B) and T_2-weighted (C) MRI and [^{11}C](*R*)-PK11195 PET (overlaid on to T_1-weighted MRI) (D) of Patient 9 show lesions in all different spin-echo MRI sequences that partially overlap with areas of significantly increased [^{11}C](*R*)-PK11195 binding (red arrow).The white arrow points to a 'black hole' in an area that appears strongly hypointense in the T_1-weighted MRI and has little binding of [^{11}C](*R*)-PK11195. Note, however, that a similar black hole (yellow arrowhead) adjacent to the right occipital horn of the lateral ventricle shows significant [^{11}C](*R*)-PK11195 binding. (E–F) Demonstration of the definition of the MRI lesion load masks in Patient 9 (purple, T_1-weighted MRI lesions excluding black holes; blue, black hole only; green, gadolinium-enhancing areas; dark grey (in F), T_2-weighted MRI lesions; red, areas of overlap between significantly increased [^{11}C](*R*)-PK11195 binding and MRI-defined areas of pathology); yellow, areas of increased [^{11}C](*R*)-PK11195 binding and no overlap with any MRI-defined pathology. (G) Average percentage volume of the MRI-defined lesions overlapping with increased [^{11}C](*R*)-PK11195 binding. The red square represents Patient 8 and the red triangle Patient 6, who were both in relapse at the time of the scans. The yellow diamond represents Patient 9, who had secondary progressive multiple sclerosis. T1*, black holes.

microglia, has revealed increased activity not only in gadolinium enhancing lesions but also in normal-appearing white matter and deep grey matter nuclei (Figure 7.25; Banati *et al* 2000; Debruyne *et al* 2003). While this marker may be of value for monitoring disease course and therapeutic intervention, neither PET nor SPECT currently have a role to play in the diagnosis of multiple sclerosis.

Ultrasonography

Based on the emerging evidence that brain atrophy is a feature of multiple sclerosis, transcranial sonography has been applied to the investigation of ventricular dimensions in multiple sclerosis. In a study of 38 patients who were followed for 2 years, there was a significant increase in the width of the third ventricle (Kallmann *et al* 2004). The measurements of the third ventricle obtained by sonography correlated well with those measured from MRI scans and a correlation was observed between disability and third ventricle width not only in this study but also in an earlier report on 74 patients (D. Berg *et al* 2000). Whilst transcranial sonography has no role in diagnosis, the authors of these studies suggested that it could provide an inexpensive test for monitoring the course of brain atrophy in multiple sclerosis.

Myelography

Myelography was once the only certain method for excluding a compressive lesion in patients presenting with a spinal cord syndrome, but the advent of MRI has rendered this investigation

largely obsolete. It should now only be required when MRI is contraindicated (patients with cardiac pacemakers) or impossible to perform (extreme obesity preventing the subject from entering the scanner or the subject having metal implants).

Retinal nerve fibre layer imaging

A relatively recent development has been the introduction of noninvasive measurement of thickness in the retinal nerve fibre layer using optical coherence tomography. This provides cross-sectional imaging of internal tissue microstructure by measuring the echo time delay of back-scattered infrared light using an interferometer and a low coherence light source. It is therefore somewhat analogous to ultrasound imaging except that light is used instead of sound. Using an early model of optical coherence tomography, Parisi *et al* (1999) described thinning of the retinal nerve fibre layer in multiple sclerosis patients who had a previous episode of optic neuritis. More recently, Trip and colleagues (2005) quantified both retinal nerve fibre layer thickness and visual function in 25 patients who had incomplete visual recovery after an attack of unilateral optic neuritis and compared the findings with those seen in 15 healthy controls. The retinal nerve fibre layer thickness was reduced by a mean of 33% in the patients' affected eye compared with healthy controls and in patients there was a significant correlation between the extent of fibre loss and the degree of impairment of visual function. Although the technique is unlikely to have a major role in diagnosis, it has promise as a non-invasive tool to monitor axonal loss and its prevention, in optic neuritis and – possibly – multiple sclerosis.

Clinically isolated syndromes

A central element in the power of MRI as a diagnostic aid is its ability to detect clinically 'silent' lesions as well as those expressed in the acute relapse. Nowhere is this better demonstrated than in the assessment of patients with clinically isolated lesions of the type seen in multiple sclerosis. The responsible symptomatic lesions are also usually readily demonstrated.

Optic neuritis

In optic neuritis, abnormalities of the optic nerve can be detected in the acute stage in >95% of patients (Gass *et al* 1996) if a phased array local coil or a conventional head receiver coil are used, together with an appropriate sequence to suppress the signal from orbital fat such as short inversion time inversion recovery (STIR), or fat suppressed T_2-weighted fast spin echo (Figure 7.26). Coronal imaging with high resolution is the best way of depicting optic nerve involvement. Enhancement is usual during the acute attack (Youl *et al* 1991b). In a large study, Kupersmith *et al* (2002) reported the presence of gadolinium enhancement of the optic nerve in 101/107 patients with acute optic neuritis. When the enhancement was more extensive or involved the optic canal, there were greater visual deficits apparent during the acute stage but the location and length of enhancement were not predictive of visual recovery. Enhancement of the optic nerve was observed in 27/28 (97%) cases using triple-dose gadolinium in a recent study of patients within 4 weeks of the onset of optic neuritis (Hickman *et al* 2004a). The enhancement is usually seen as a homogeneous region within the optic nerve though we have sometimes seen it to be more apparent involving the outer nerve and/or sheath (Figure 7.27). The length of optic nerve lesions ranges from a few millimetres to the whole nerve. There is some evidence that longer lesions, when seen on the STIR sequence, and when they include the intracanalicular portion of the optic nerve, are associated with poorer visual outcome (Kapoor *et al* 1998; Miller *et al* 1988c). Exceptionally, the abnormal signal can extend back to a swollen chiasm (Figure 7.28; Cornblath and Quint 1997). Acute lesions more often display swelling whereas it is not unusual to see a degree of optic nerve atrophy in chronic lesions.

Figure 7.26 Coronal T_2-weighted fast spin echo image through the orbits of a patient with unilateral optic neuritis. High signal is seen in the affected optic nerve.

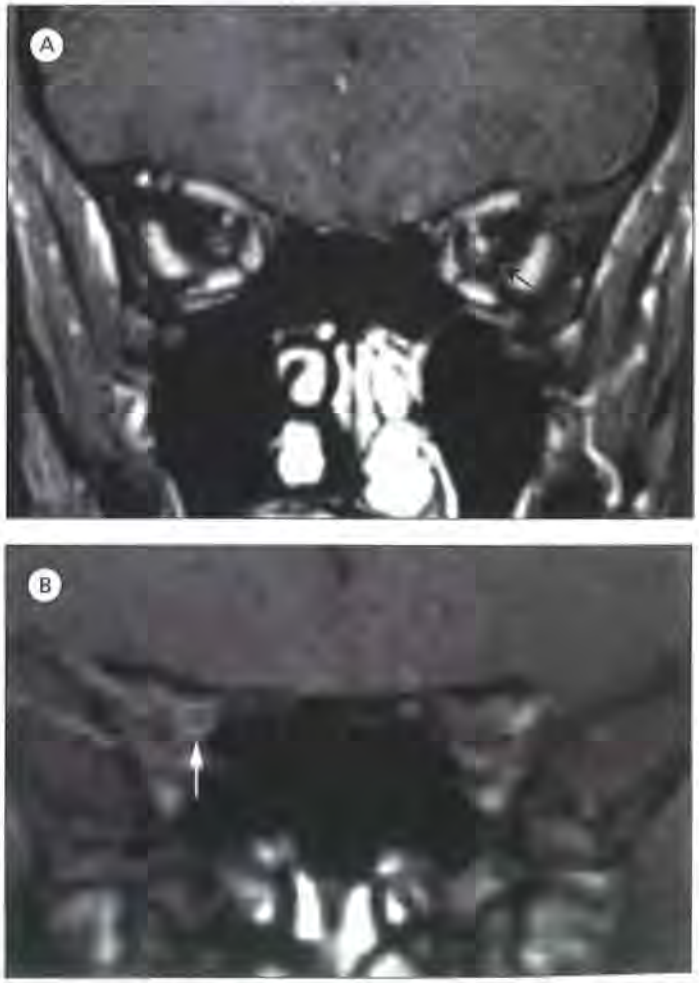


Figure 7.27 Triple-dose gadolinium enhanced coronal T_1-weighted MRI in two cases of acute optic neuritis. (A) Homogeneous enhancement of the left optic nerve. (B) Enhancement of the right optic nerve sheath (arrowed).

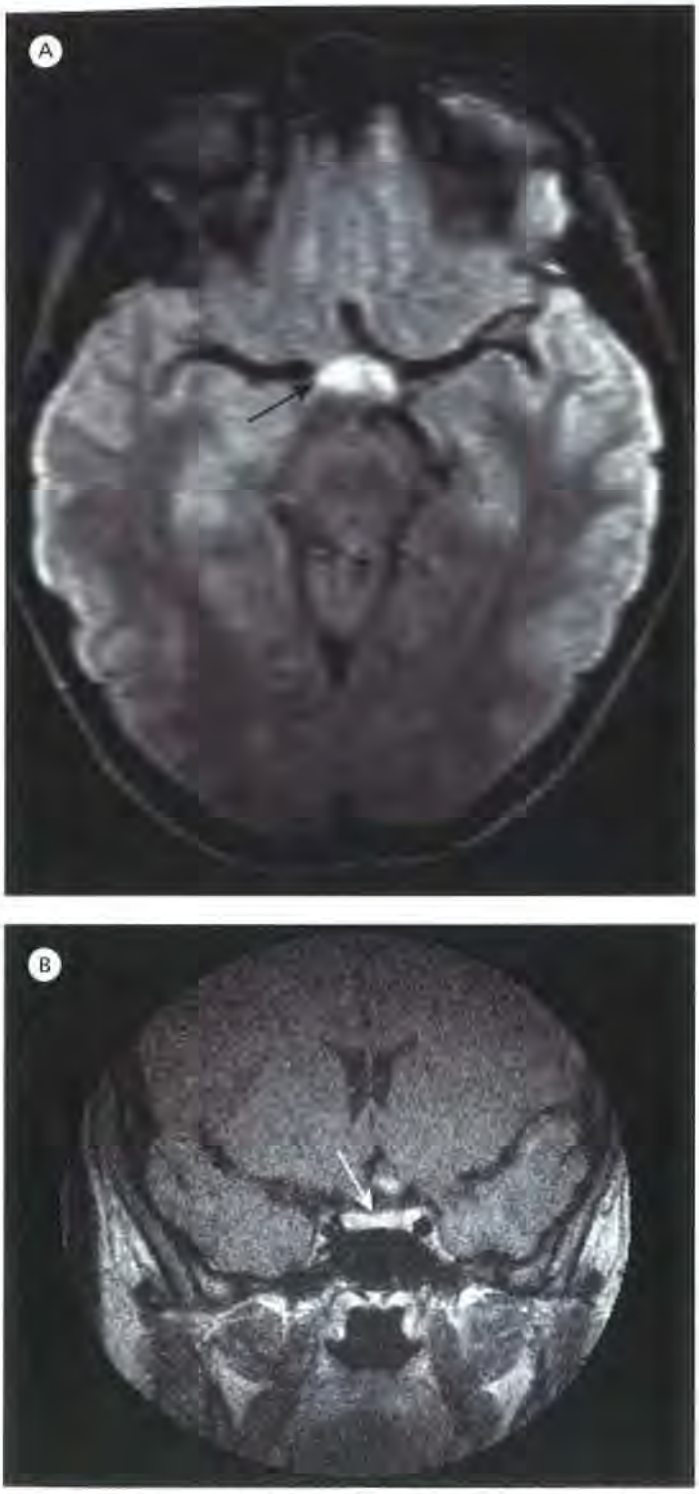


Figure 7.28 Chiasmal involvement in optic neuritis (arrows). (A) T_2-weighted MRI. (B) Gadolinium enhanced T_1-weighted MRI.

In a recent serial study using quantitative measures of optic nerve size, we observed a mean 20% increase in cross-sectional area of the acutely symptomatic nerve and a mean 12% decrease in its area after 1 year, when compared with the clinically unaffected nerve (Figure 7.29; Hickman *et al* 2004b). Magnetization transfer imaging has shown decreases in optic nerve magnetization transfer ratio following an attack of optic neuritis (Inglese *et al* 2002b; Thorpe *et al* 1995). A serial study reported that magnetization transfer ratio reached its nadir after about 6–9 months and then increased slightly by 1 year, possibly reflecting remyelination (Hickman *et al* 2004c)

Brainstem lesions

MRI detects the causative lesion of isolated brainstem syndromes in about 90% of cases, and provides good anatomical correlation with the clinical features (Bronstein *et al* 1990a; 1990b; Ormerod *et al* 1986). For example, in patients with an acute onset of diplopia and an internuclear ophthalmoplegia, it is usual to find an area of high signal in the region of the medial longitudinal fasciculus. As at other sites, the areas of increased signal almost always persist after full clinical recovery. Most, but not all, acutely symptomatic brainstem lesions exhibit gadolinium enhancement.

Spinal cord lesions

The frequency with which the causative lesion is found in acute or chronic spinal cord syndromes was found to be rather lower in the early studies (64% for the cervical region; D.H. Miller *et al* 1987a), but it is undoubtedly higher using more modern instruments. Reflecting the sites of clinical and pathological predilection, lesions are most commonly seen in the cervical spinal cord, although any part may be affected including, exceptionally, the conus medullaris (Figure 7.30). The spatial resolution of spinal cord imaging is still not good enough to permit detailed correlations between the location of lesions and their clinical expression down to the level of individual white matter tracts. Nevertheless, broad correlations are possible, such as between lesions involving the dorsolateral part of the mid- or lower cervical cord and the useless (deafferented) hand syndrome (see Figure 7.31; D.H. Miller *et al* 1987a), ipsilateral lesions and partial Brown–Sequard syndrome, or posterior lesions and Lhermitte's symptom. A rather surprising finding in spinal cord imaging has been the frequency with which swelling is observed. This was sometimes revealed by myelography in the pre-MRI era but the procedure was infrequently performed in acute myelopathy because of its invasive nature, and was less sensitive than MRI in detecting minor focal changes in size such as are now seen routinely. Swelling is observed in many acutely symptomatic lesions but may persist for several months. The pattern of gadolinium enhancement in cord lesions is similar to that seen in the brain, in that both uniform and ring-like patterns are seen. Occasionally, one sees a rather patchy lesion extending over several segments but, more typically, the lesions are less than one segment in length. It is rare for demyelinating cord lesions to display T_1 hypointensity. In contrast, patients with acute transverse myelitis often exhibit lesions in which there is marked swelling with signal change extending over multiple segments of the cord, sometimes with T_1 hypointensity.

Additional lesions and the risk for multiple sclerosis

There are many reports of clinically silent lesions involving cerebral white matter and spinal cord at the time of presentation with clinically isolated syndromes (Figure 7.32). The frequency varies somewhat, but overall is about 60–70% in the brain (L.D. Jacobs *et al* 1986a; Ormerod *et al* 1987) and 30% in the

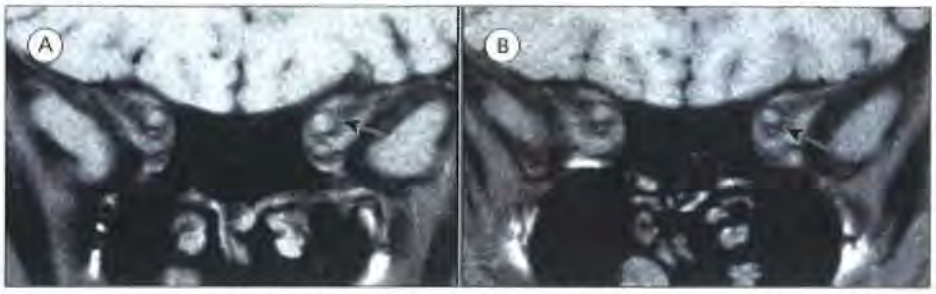


Figure 7.29 Coronal fast FLAIR images through the orbits. (A) During an attack of left optic neuritis and (B) 12 months after the episode of left optic neuritis. The affected nerve is swollen acutely and atrophic 1 year later (arrows).

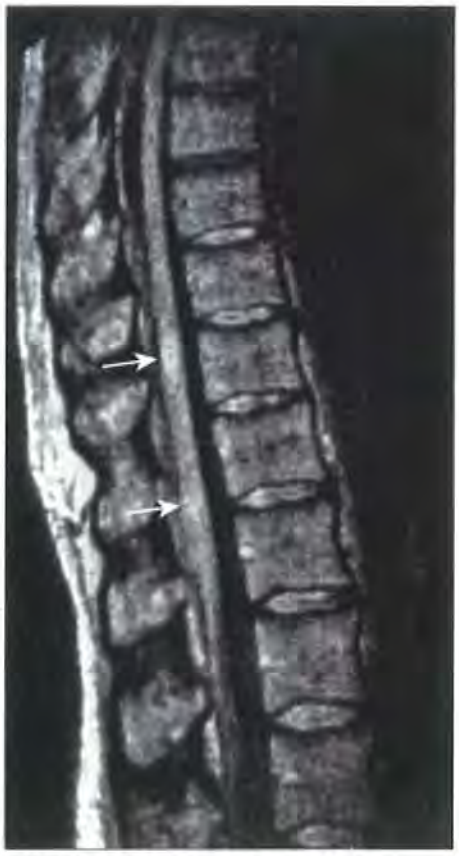


Figure 7.30 T_2-weighted MRI showing a conus lesion (lower arrow) in a patient with multiple sclerosis; there is another lesion (upper arrow) two segments higher up.

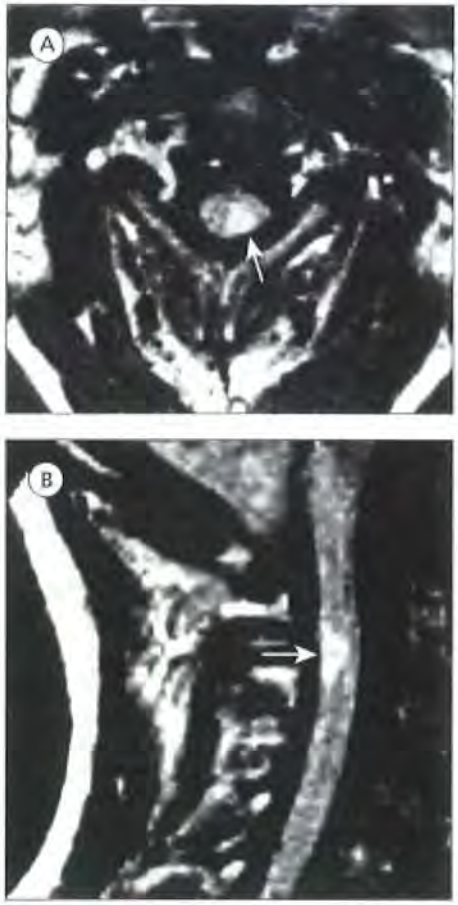


Figure 7.31 T_2-weighted scan. (A) Axial and (B) sagittal MRI showing a posterior cervical cord lesion (arrows) in a multiple sclerosis patient with deafferentation of the upper limb (useless hand of Oppenheim).

spinal cord (Dalton *et al* 2004b; O'Riordan *et al* 1998a). The presence and number of such lesions is of predictive value for the development of multiple sclerosis in the next 1–5 years (Beck *et al* 1993b; Campi *et al* 1995; B. Ford *et al* 1992; Frederiksen *et al* 1991a; Ghezzi *et al* 1999; L.D. Jacobs *et al* 1997; Martinelli *et al* 1991; D.H. Miller *et al* 1988a; 1989b; Morrissey *et al* 1993a; Söderström *et al* 1994a; 1998; Tas *et al* 1995). In a 3-year follow-up study of 52 patients presenting with an isolated acute partial myelopathy, Cordonnier *et al* (2003) confirmed numerous other studies in showing that brain MRI abnormalities are predictive for conversion to clinically definite multiple sclerosis. Additional predictive features were the presence of sensory symptoms, cerebrospinal fluid oligoclonal bands and posterolateral spinal cord lesions.

The cohort followed for the longest time to date is reported from the National Hospital in London. By 5 years after presentation, 72% of those with additional lesions had developed clinically definite multiple sclerosis compared with 6% of patients without abnormalities at other sites (Morrissey *et al* 1993a). After 10 years, the gap for the whole group had narrowed slightly (83% versus 11%), but the significantly better prognosis for those without cerebral lesions at presentation was

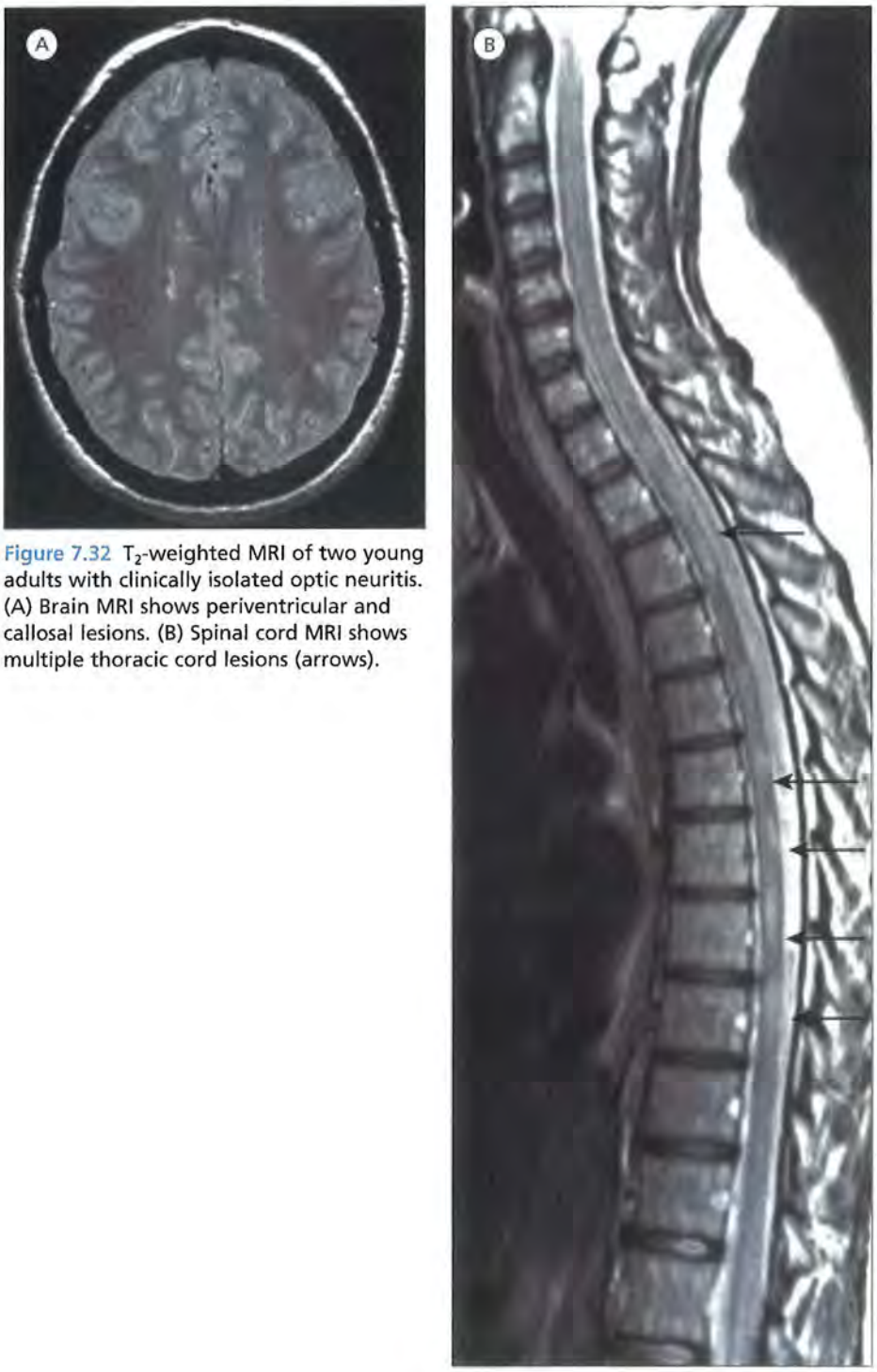


Figure 7.32 T_2-weighted MRI of two young adults with clinically isolated optic neuritis. (A) Brain MRI shows periventricular and callosal lesions. (B) Spinal cord MRI shows multiple thoracic cord lesions (arrows).

still striking (O'Riordan *et al* 1998). After 14 years, 88% of patients with an abnormal scan had developed clinically definite multiple sclerosis compared with 19% of those with normal MRI at presentation (Brex *et al* 2002). Caution is needed in interpreting the precise proportions converting to multiple sclerosis because about one-third of patients were lost to follow-up. In the North American Optic Neuritis treatment trial cohort, follow-up after 10 years revealed conversion to clinically definite multiple sclerosis in 56% of patients who had an abnormal brain MRI at presentation and in 22% with a normal scan (Optic Neuritis Study Group 2003). Taken together, these two long-term follow-up studies, of 10 and 14 years duration, indicate that the majority of patients with clinically isolated syndromes and brain MRI abnormalities will develop clinically definite multiple sclerosis (60–80%), whereas a considerably smaller proportion (about 20%) with a normal scan are seen to convert after prolonged follow-up.

The predictive value of the Barkhof/Tintoré criteria (see above) were tested in a group of 309 patients with a first clinical episode followed up for 2 years as part of a therapeutic trial (Barkhof *et al* 2003b). In the placebo arm of the study, the rate of conversion to clinically definite multiple sclerosis was

23% in subjects who had at least two MRI features, 38% in those with three components, and 57% when all four features were present. In a further study, Tintoré *et al* (2001) demonstrated that the original Barkhof MRI criteria, when applied to 112 patients with a clinically isolated syndrome, were more specific for multiple sclerosis (specificity 70%) than either the Paty *et al* (1988) or Fazekas *et al* (1988) MRI criteria (both 51%) or the presence of cerebrospinal fluid oligoclonal bands (43%).

The McDonald criteria proposed two additional modifications to the necessary evidence for dissemination in space. The first allowed the combination of two brain MRI lesions and cerebrospinal fluid oligoclonal bands as sufficient features. However, application of this modification to a cohort of clinically isolated syndrome patients showed them to have a rather low specificity (63%) for developing clinically definite multiple sclerosis after 3 years (Tintoré *et al* 2003). The second modification was to allow one spinal cord lesion to substitute for one brain lesion. Dalton *et al* (2003b) investigated the effect of this change in a group of 115 patients with clinically isolated optic neuritis who underwent combined brain and cord imaging. Although they found that 31 (27%) had clinically silent lesions in the cord, all but four of these individuals had additional brain lesions. Not surprisingly, allowing a cord lesion to substitute for a brain lesion had little impact on the frequency with which multiple sclerosis was diagnosed at follow-up. It follows that there is little if any role for spinal MRI in the routine investigation of patients with isolated optic neuritis, although future reviews of the diagnostic criteria might usefully consider whether spinal MRI findings could be included more effectively than is currently the case.

Serial scanning and the risk for multiple sclerosis

One essential diagnostic criterion for multiple sclerosis is the appearance of new lesions over time. MRI is currently the most powerful method available for obtaining this information, not least because the annual frequency with which new lesions appear, calculated from serial scanning in patients with established relapsing–remitting and secondary progressive disease at monthly intervals, is five- to ten-fold higher than that determined on the basis of clinical relapse – and occasionally much higher. When there is uncertainty about the diagnosis of multiple sclerosis early in its course, it is often worth repeating the scan after 6–12 months. Although not specific for multiple sclerosis, the appearance of a new lesion may be decisive in the appropriate clinical context.

In patients with clinically isolated syndromes, MRI evidence for dissemination in time is incorporated in contemporary criteria for the diagnosis of multiple sclerosis (W.I. McDonald *et al* 2001). These require evidence for a change appearing 3 or more months after the clinical episode (Figure 7.33). This can be either gadolinium enhancement or a new T_2 lesion. Subsequently the predictive value of serial MRI has been reported for cohorts of patients based in London and Barcelona with a clinically isolated syndrome, and followed independently and prospectively from onset. The studies show that either new gadolinium enhancement or T_2 lesions after 3 months (Brex *et al* 2001a; Dalton *et al* 2002a; 2003a), or new T_2 lesions after 1 year (Dalton *et al* 2002a; Tintoré *et al* 2003), carry high specificity for developing clinically definite multiple sclerosis after 3 years. The requirement for dissemination in both space and time increased the specificity for developing clinically definite multiple sclerosis compared with merely requiring evidence for dissemination in space on the first scan. These findings suggest that the new imaging criteria for multiple sclerosis are reliable when applied in an appropriate clinical setting by experienced clinical teams, and that requiring evidence for dissemination in time is, as expected, an important element in ensuring that the diagnosis is accurate. It is nevertheless worth adding that the new criteria (W.I. McDonald *et al* 2001) allow either MRI or clinical evidence for dissemination in space and time to secure the diagnosis of multiple sclerosis. Therefore, some patients can be diagnosed without fulfilling the new MRI criteria for dissemination in time and space. In the study of clinically isolated syndromes by Dalton *et al* (2002b), after 1 year of follow-up, 22 had developed multiple sclerosis by MRI criteria alone, 13 by both MRI and clinical criteria, and three by clinical criteria alone.

MRI lesions and the risk for disability

Filippi *et al* (1994) correlated the amount of affected cerebral tissue at presentation in individuals with isolated syndromes with subsequent disability in those who developed multiple sclerosis during follow-up over 5 years. In the London cohort studied for 14 years, the strongest correlation was between concurrent change in T_2 lesion volume and disability developing during the first 5 years. Thereafter, changes in T_2 volume appeared to make little impact on the future clinical course (Brex *et al* 2002). The strength of the correlation between T_2 volume increased over the first 5 years, and disability at year 14 remained modest ($r = 0.61$), suggesting that some but not most long-term disability can be related to early lesion load. Those who developed secondary progressive disease had – as a group – larger lesion loads at 5 years than those who exhibited a benign course. However, considerable inter-individual variations were also observed, some patients showing minimal later disability despite exhibiting large early lesion loads, whereas others developed secondary progressive disease in the context of quite small lesion loads at presentation. In another cohort of 42 patients followed for 8 years after onset with a clinically isolated syndrome, disability at follow-up was significantly related to total T_2 lesion load and infratentorial lesion load at presentation (Minneboo *et al* 2004). While these findings suggest that treatments that suppress the accumulation of T_2 lesions in early relapsing disease have the potential to modify the long-term course with respect to the development of disability, T_2 load *per se* is not enough to guide treatment decisions in the individual patient. It should also be remembered that mechanisms underpinning the relationship between MRI lesions and long-term disability are not well understood.

Normal-appearing brain tissue abnormalities detected by MRI

Some recent investigations have reported the presence of a variety of quantitative MRI abnormalities in white and/or grey matter with normal appearance in patients with clinically isolated syndromes, or very early in the course of relapsing–remitting multiple sclerosis. The abnormalities include a reduction in magnetization transfer ratio (Griffin *et al* 2002a; Iannucci

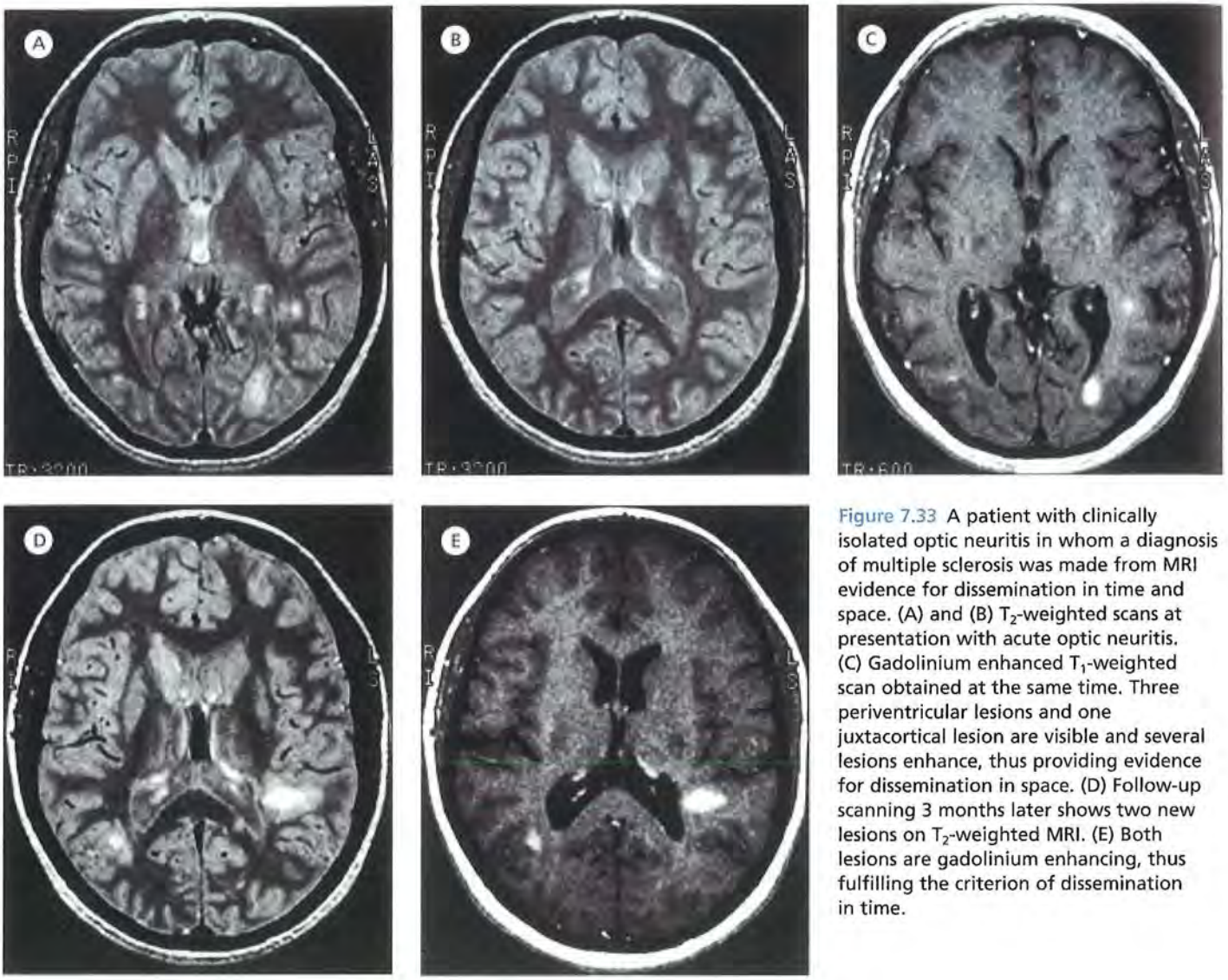


Figure 7.33 A patient with clinically isolated optic neuritis in whom a diagnosis of multiple sclerosis was made from MRI evidence for dissemination in time and space. (A) and (B) T_2-weighted scans at presentation with acute optic neuritis. (C) Gadolinium enhanced T_1-weighted scan obtained at the same time. Three periventricular lesions and one juxtacortical lesion are visible and several lesions enhance, thus providing evidence for dissemination in space. (D) Follow-up scanning 3 months later shows two new lesions on T_2-weighted MRI. (E) Both lesions are gadolinium enhancing, thus fulfilling the criterion of dissemination in time.

et al 2000b), an increase in T_1 relaxation time (Griffin *et al* 2002a; 2002b), increased diffusivity (Gallo *et al* 2005) and – on MR spectroscopy – a reduction in *N*-acetyl aspartate (Chard *et al* 2002a; 2002b; 2002c; Filippi *et al* 2003) and an increase in myoinositol (Figure 7.34; Chard *et al* 2002b; Fernando *et al* 2004). In addition, progressive ventricular enlargement and grey matter atrophy have been detected in patients evolving from a clinically isolated syndrome to multiple sclerosis within 1–3 years (Figures 7.20 and 7.35; Dalton *et al* 2002b; 2004a). Whilst such studies have collectively emphasized that there is a diffuse and progressive pathological process occurring from the earliest stages of the disease, and by implication raising the potential for some of the quantitative imaging measures having a useful prognostic role (although that can only be determined through follow-up), the abnormalities described are not sufficient to provide diagnostic utility. They are subtle, have not always been reproduced in different centres, are not sufficiently studied in other conditions, and are difficult to implement with adequate quality control on a routine basis.

Other central nervous system disorders

The differential diagnosis of multiple sclerosis and MRI findings encountered in many of these disorders are discussed in Chapter 8. Here, we confine ourselves to the MRI findings encountered in two 'generic' categories of neurological disease that are sometimes difficult to separate by clinical and/or MRI findings from multiple sclerosis: cerebrovascular (small vessel) disease and cerebral tumour.

Nonspecific age-related changes caused by small vessel disease

A common source of difficulty is the presence of small areas of high signal in the cerebral white matter of older patients (see Figure 7.4). With modern high field instruments such changes are seen with increasing frequency in healthy individuals aged >40 years. In our series of 131 apparently healthy individuals aged 17–79 years, more lesions were seen at 1.5 than at

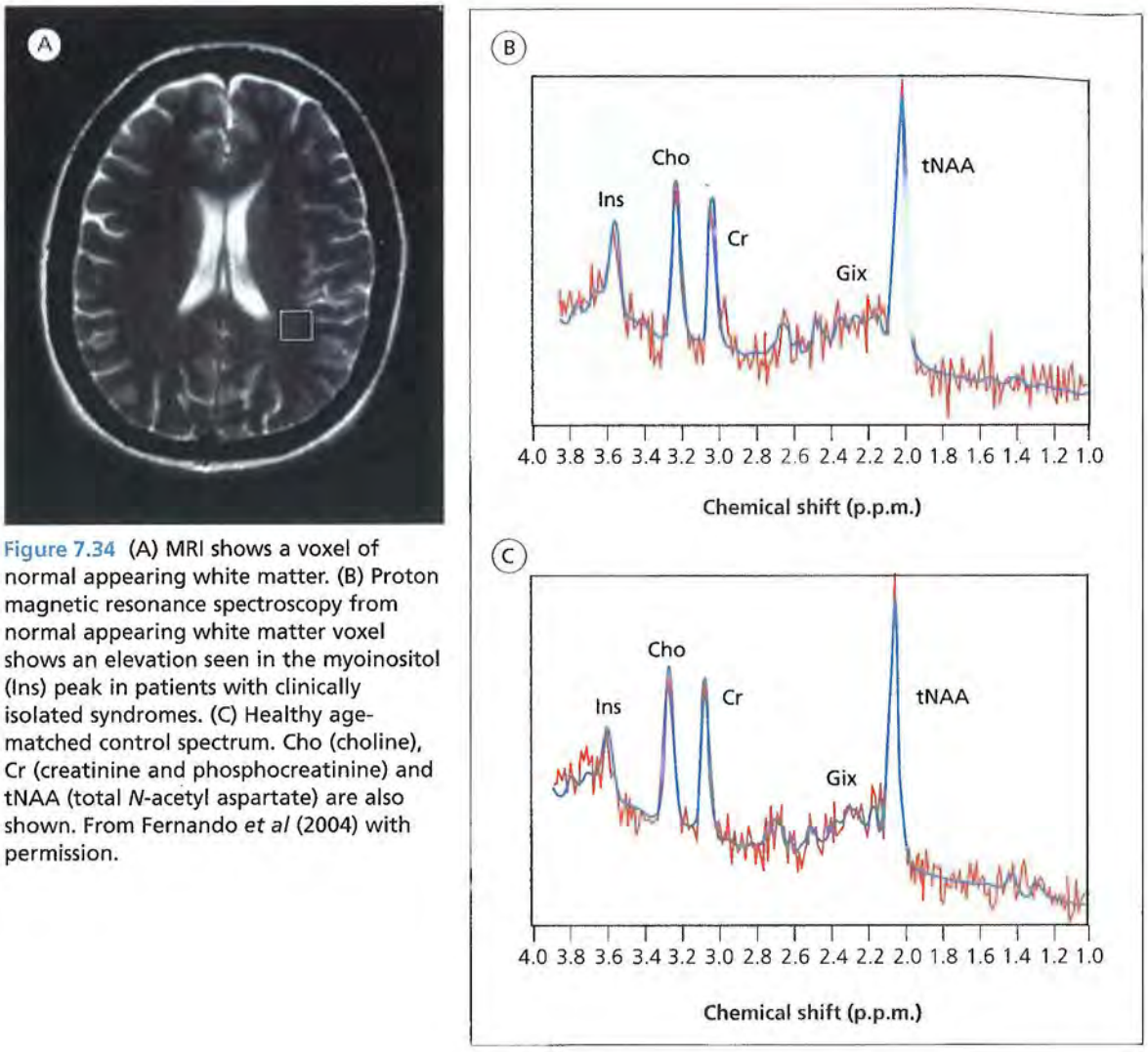


Figure 7.34 (A) MRI shows a voxel of normal appearing white matter. (B) Proton magnetic resonance spectroscopy from normal appearing white matter voxel shows an elevation seen in the myoinositol (Ins) peak in patients with clinically isolated syndromes. (C) Healthy age-matched control spectrum. Cho (choline), Cr (creatinine and phosphocreatinine) and tNAA (total *N*-acetyl aspartate) are also shown. From Fernando *et al* (2004) with permission.

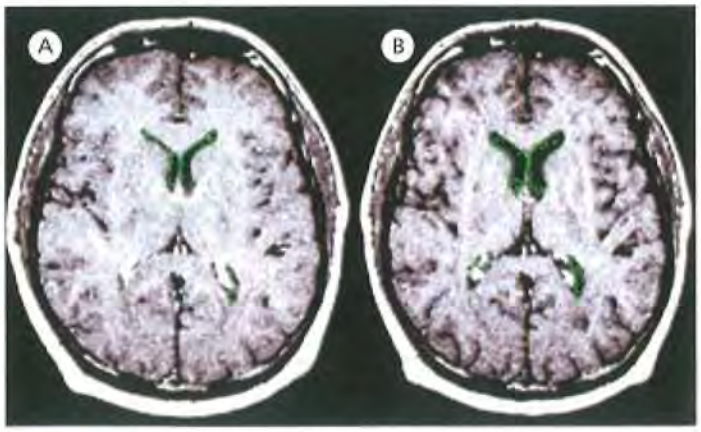


Figure 7.35 T_1-weighted MRI scans in a patient who presented with isolated optic neuritis and went on to develop multiple sclerosis during the follow-up year. (A) Obtained at presentation and (B) 1 year later. Significant ventricular enlargement – indicating loss of brain tissue – has occurred during follow-up. The green line indicates the lateral ventricle margins; the measure of ventricular volume was generated using an automated boundary detection method. From Dalton *et al* (2002b) with permission.

0.5 Tesla field strength. In those under 50 years of age, four (4.5%) had multifocal white matter abnormalities. Eight (30%) of those aged between 50 and 59 years had abnormal scans. In the 13 subjects aged 60 or over, seven (54%) had abnormal MRI examinations (D.H. Miller *et al* 1997). These appearances are nonspecific and, although their pathogenesis is not fully understood, they probably reflect small areas of ischaemia in the elderly (Kirkpatrick and Hayman 1987). The characteristics of their location, size and frequency help to make the distinction from the lesions of multiple sclerosis. Age-related lesions tend to be smaller and situated away from the ventricles, often in the subcortical white matter. Sometimes an appearance of multiple small lesions in a linear distribution is seen in the centrum semiovale, possibly indicating watershed ischaemia. When periventricular abnormality occurs, it may have a smooth contour – unlike the irregular and asymmetrical appearances associated with periventricular plaques of demyelination. The basal ganglia are quite frequently involved in small vessel disease, whereas MRI-detectable lesions in this location are uncommon (<10%) in multiple sclerosis (D.H. Miller *et al* 1997; Ormerod *et al* 1987). Conversely, although commonly involved in multiple sclerosis, the corpus callosum (Gean-Marton *et al* 1991) and spinal cord (Bot *et al* 2002) are rarely affected by age-related vascular changes. Thorpe *et al* (1993) observed only a single abnormality in the spinal cords of 45 apparently healthy individuals, and none in the 17 individuals aged over 50 years. Thus, MRI of the spinal cord is often helpful when there is diagnostic doubt in the older decades. Several sets of criteria have been devised to help distinguish the imaging appearances of multiple sclerosis and small vessel disease, most particularly those of Paty *et al* (1988) and Fazekas *et al* (1988). It should be noted that the Barkhof/Tintoré and McDonald criteria for multiple sclerosis, although useful in defining the risk for developing clinically definite multiple sclerosis in patients with a single clinical episode of suspected demyelination, have not been tested in a study that compares multiple sclerosis and small vessel disease. Conversely, the Fazekas criteria have been extensively validated in this context. It should be emphasized that although these criteria have proved relatively specific for multiple sclerosis when compared with subjects with small vessel disease, they are not pathognomonic, and some patients with vascular disease are encountered in whom all of the Fazekas criteria features are met.

The abnormalities found in apparently healthy individuals are usually not extensive but occasionally cannot be distinguished from those seen in established multiple sclerosis. The occasional demonstration of multiple lesions in healthy individuals is in keeping with the reports of unexpectedly finding the plaques of multiple sclerosis at post mortem (Ghatak *et al* 1974; Gilbert and Sadler 1983; Phadke and Best 1983).

In contrast to these focal cerebral changes, there are characteristically extensive confluent changes in the cerebral white matter in dementia associated with advanced cerebral vascular disease (Figure 7.36). The condition is sometimes referred to as 'Binswanger's disease' and the imaging appearance is included under the somewhat ill-defined term 'leucoariosis' (Hachinski *et al* 1987). Such confluent changes in the cerebral white matter may also be seen in apparently healthy individuals of advanced years. All these appearances can be indistinguishable from those seen in advanced multiple sclerosis. A feature that aids the distinction is characteristic sparing of subcortical U-fibres in Binswanger's disease, whereas the lesions of multiple sclerosis frequently involve this region.

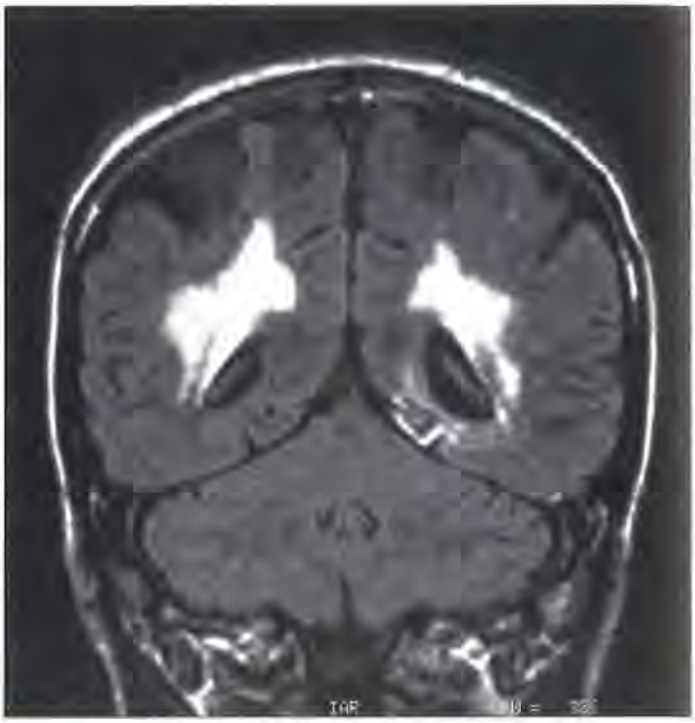


Figure 7.36 Coronal T_2-weighted MRI of a subject with hypertension and dementia. There is extensive periventricular and deep white matter abnormality with sparing of subcortical U-fibres (Binswanger's subcortical arteriosclerotic leucoencephalopathy). Kindly provided by Professor Tarek Yousry and Dr Ralf Jager.

Tumours

Intrinsic neoplasms of the nervous system are rarely confused with multiple sclerosis. Occasionally, however, focal swelling of the brain (Figure 7.9) or spinal cord occurring in the context of acute inflammatory demyelination, closely mimics a tumour. The symptoms and signs of raised intracranial pressure may even be present. That such appearances can be the result of multiple sclerosis lesions – sometimes showing necrosis, cyst formation and extensive oedema – has been confirmed histologically (Youl *et al* 1991a). In addition to tumour or demyelination, a large ring enhancing mass lesion will include brain abscess in the differential diagnosis. The presence of other clinical and MRI features of multiple sclerosis point to the correct diagnosis and, in this situation, it is usually appropriate to defer surgery while treating with corticosteroids and performing serial scans to see whether there is sustained regression of the mass with symptomatic improvement.

The need occasionally to biopsy these cases as part of clinical management has, by serendipity, allowed a much improved understanding of the early pathological features of multiple sclerosis and histological validation of the acute imaging appearances (see Chapter 12). A major international research initiative is currently using biopsy or autopsy material to investigate immunopathogenic mechanisms and MRI/pathology correla-

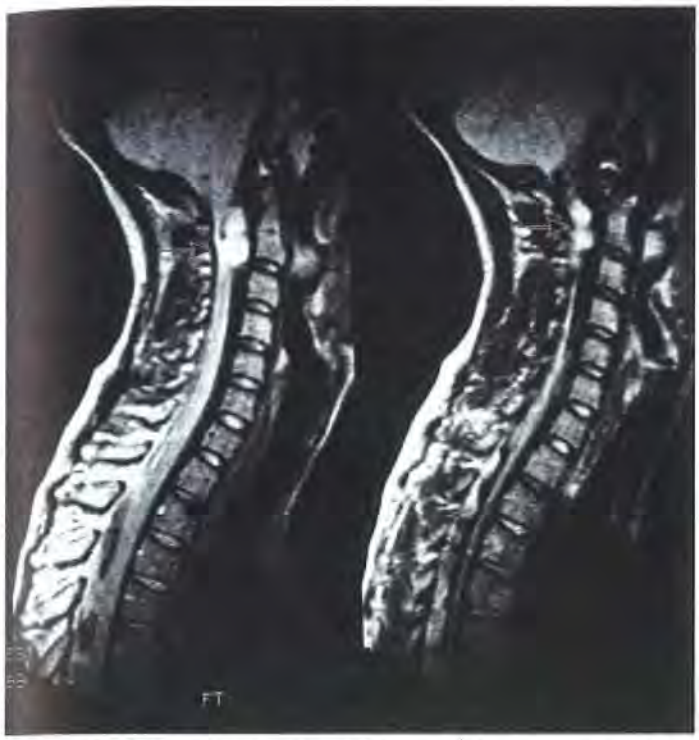


Figure 7.37 MRI of the craniocervical region showing compression of the cord by a neurofibroma (arrows).

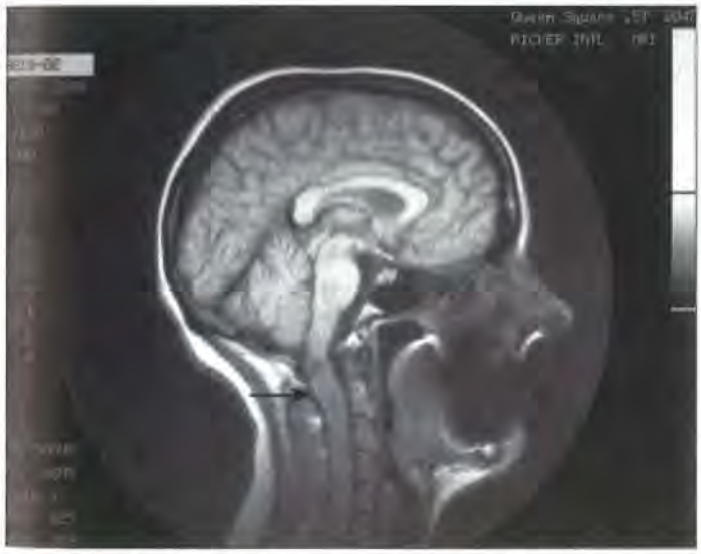


Figure 7.38 MRI in a patient with relapsing–remitting neurological symptoms affecting a single site (the cervical cord) in whom the erroneous diagnosis of multiple sclerosis had previously been made. The lesion was an ependymoma (arrow).

tions. Initial reports have emphasized the occurrence of four types of active lesion in multiple sclerosis (Lucchinetti *et al* 2000). As discussed in Chapter 12, the most prevalent are Types I and II, which respectively exhibit features suggesting T-cell-mediated and T-cell/antibody-mediated demyelination with myelin as the principal target. Type III and IV lesions show features suggestive of ischaemia and a primary dystrophic process

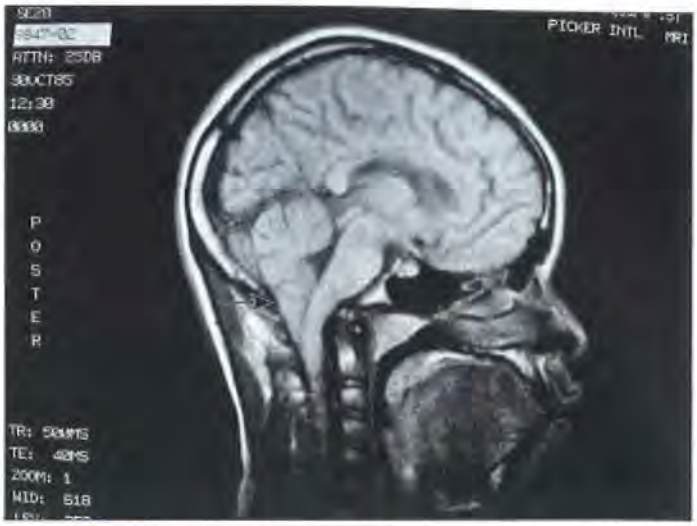


Figure 7.39 Herniation of the cerebellar tonsils demonstrated by MRI (arrow) producing intermittent neurological symptoms misdiagnosed for several years as multiple sclerosis.

of oligodendrocytes, respectively. These reports emphasize that individual patients exhibit the same, single type of active lesion. It is as yet less clear how this form of lesion staging relates to clinical prognosis or MRI findings, although a more favourable response to plasma exchange has been reported in patients who exhibit Type II lesions (Keegan *et al* 2004). Interpretation of the neuropathological data is complicated by the fact that a large proportion of multiple sclerosis lesions that require biopsy are, inevitably, atypical being unusually large and with aggressive clinical manifestations.

Tumours arising outside (e.g. meningioma and neurofibroma, Figure 7.37) or inside (e.g. ependymoma, Figure 7.38) the neuraxis, and congenital disorder, such as the Arnold–Chiari malformation (Figure 7.39), all of which can simulate primary progressive multiple sclerosis, are readily distinguished by MRI (see Chapter 8 for further clinical discussion of these differential diagnoses).

EVOKED POTENTIALS

The exploration of human central nervous system function by evoked potential methods originates from the observations of Dawson (1947a; 1947b). The impetus to apply these techniques to multiple sclerosis came from two directions. First, was the demonstration that, as in the peripheral nervous system, central demyelination also slows conduction. This slowing serves, in optimal conditions, to distinguish the underlying pathological process from axonal degeneration where surviving conduction is normal or of only slightly reduced velocity (see Chapter 13). Secondly, peripheral nerve conduction studies from the 1960s proved useful in distinguishing demyelinating from degenerative peripheral neuropathies. In 1971, it occurred to one of us (WIMcD) that evoked potential methods might be used in a similar way, and with Martin Halliday an evoked potential study of optic neuritis was undertaken (Halliday *et al* 1972; see Chapter 1). Somatosensory evoked potentials had already been

used to a limited extent to investigate the pathophysiology of central nervous system dysfunction in a variety of disorders, including multiple sclerosis (J.B. Baker *et al* 1968; Halliday and Wakefield 1963; Namerow 1968b). The systematic exploitation of evoked potential techniques as diagnostic aids began, however, with the pattern reversal visual evoked potential in optic neuritis, which at once revealed a dramatic increase in latency, detectable in 90% of cases (Halliday *et al* 1972). More modest delays were soon found to be characteristic findings in somatosensory (Desmedt and Noel 1973; Fukushima and Mayanagi 1975; Small 1976; D.G. Small *et al* 1978; Trojaborg and Petersen 1979) and auditory evoked potentials (Chiappa 1980; Eisen and Odusote 1980; Robinson and Rudge 1977). Delays in the motor response evoked by electrical (Cowan *et al* 1984; Marsden 1980; Merton and Morton 1980a; 1980b; Merton *et al* 1982; Mills and Murray 1985; Rossini *et al* 1985) or magnetic (Barker *et al* 1985a; 1985b; 1986; Hess *et al* 1986; Ingram *et al* 1987) stimulation of the cortex were later observed.

Application of evoked potential techniques to the clinical assessment of patients with multiple sclerosis began right away (Halliday *et al* 1973b), and their value was at once apparent. As already pointed out, the principal contributions of evoked potentials have been to answer the questions:

- Is a clinically silent lesion present?
- Is the process of demyelination present?

One selects a pathway for the evoked potential that assesses an asymptomatic region of the nervous system. The result of the examination may of course answer both questions but, if not, a clinically affected part of the central nervous system may then be chosen for interrogation. Although the introduction of MRI from the 1980s has substantially reduced the frequency with which evoked potentials are ordered as diagnostic tools in cases of suspected multiple sclerosis, they are still of use when there is diagnostic difficulty. This applies especially to use of the visual evoked potential. A report of the Quality Standards Subcommittee of the American Academy of Neurology has recently evaluated the utility of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (Gronseth and Ashman 2000). They produced the following recommendations.

- Visual evoked potentials are probably useful to identify patients at increased risk for developing clinically definite multiple sclerosis.
- Somatosensory evoked potentials are possibly useful to identify patients at increased risk for developing clinically definite multiple sclerosis.
- There is insufficient evidence to recommend brainstem auditory evoked potentials as a useful test to identify patients at increased risk for developing clinically definite multiple sclerosis.

This sensibly conservative approach has been further tempered by the subsequently published new diagnostic criteria for multiple sclerosis, which rely more heavily on MRI evidence of dissemination in space and time to enable the diagnosis (W.I. McDonald *et al* 2001).

Evoked potentials have been infrequently used to monitor the course of established multiple sclerosis, and the advent of MRI has probably inhibited efforts to investigate serial changes in evoked potential measures. A 2-year study of a mixed cohort of 30 patients with relapsing–remitting or secondary progressive multiple sclerosis showed a modest relationship between changes in disability and visual and motor evoked potential measures but also concluded that a reliable prediction of the course of multiple sclerosis is not possible from the evoked potential measures (Fuhr *et al* 2001). The introduction of evoked potentials has been of great value in understanding the pathophysiology of central nervous system demyelination in patients, and in confirming that the detailed findings from experimental studies are reproduced in humans. We will consider each modality used for evoked potentials in some detail, partly because of their historical contribution to our understanding of multiple sclerosis, and in part because of their remaining utility (Figure 7.40).

Visual evoked potentials

It was a stroke of good fortune that the method of pattern reversal stimulation used by Halliday and his colleagues to study the cortical representation of vision was close to the optimum – as it turned out – needed to demonstrate delays in optic neuritis (Halliday *et al* 1972). The flash evoked potential is much less sensitive to the effects of demyelinating lesions in multiple sclerosis (Halliday *et al* 1972; Namerow and Enns 1972; Richey *et al* 1971; Rouher *et al* 1969) and is not now used in routine clinical practice. It has a small place in helping to determine whether any visual function remains in severely impaired individuals, and in the assessment of an intact visual pathway in individuals with hysterical blindness who elect not to fixate on a more subtle stimulus.

Although there are minor variations between laboratories, the standard technique of stimulation is to use a chequerboard pattern of black and white squares that reverses at 2 Hz and where each square subtends approximately 50 minutes of arc at the retina. The whole stimulus usually occupies 32° of the field. For special purposes, half field and central field (4°) stimuli are invaluable. Further details of the technique are given in standard works of reference (for example, Halliday 1993).

Optic neuritis

The normal pattern reversal induced visual evoked potential is dominated by a large positive wave at approximately 100 ms (P100; Figure 7.41). In the acute stage of optic neuritis, the response is decreased in amplitude or, if the visual acuity is <6/24, it is usually absent. Any surviving response is delayed. As recovery of vision occurs, the amplitude increases and a delayed response with a well-preserved waveform is seen in 90% of patients (Halliday *et al* 1973a). The mean delay is approximately 35 ms (Halliday *et al* 1973a). Delays persist in about 90% of adults, although the latency may decrease after many months, sometimes reverting to normal values (see Chapter 13 and Figure 7.42). In a follow-up study lasting 4 years, W.B. Matthews and Small (1979), found that the latency returned to normal in 19% of subjects. Hely *et al* (1986b) observed a similar rate of recovery. Brusa *et al* (2001) also noted shortening

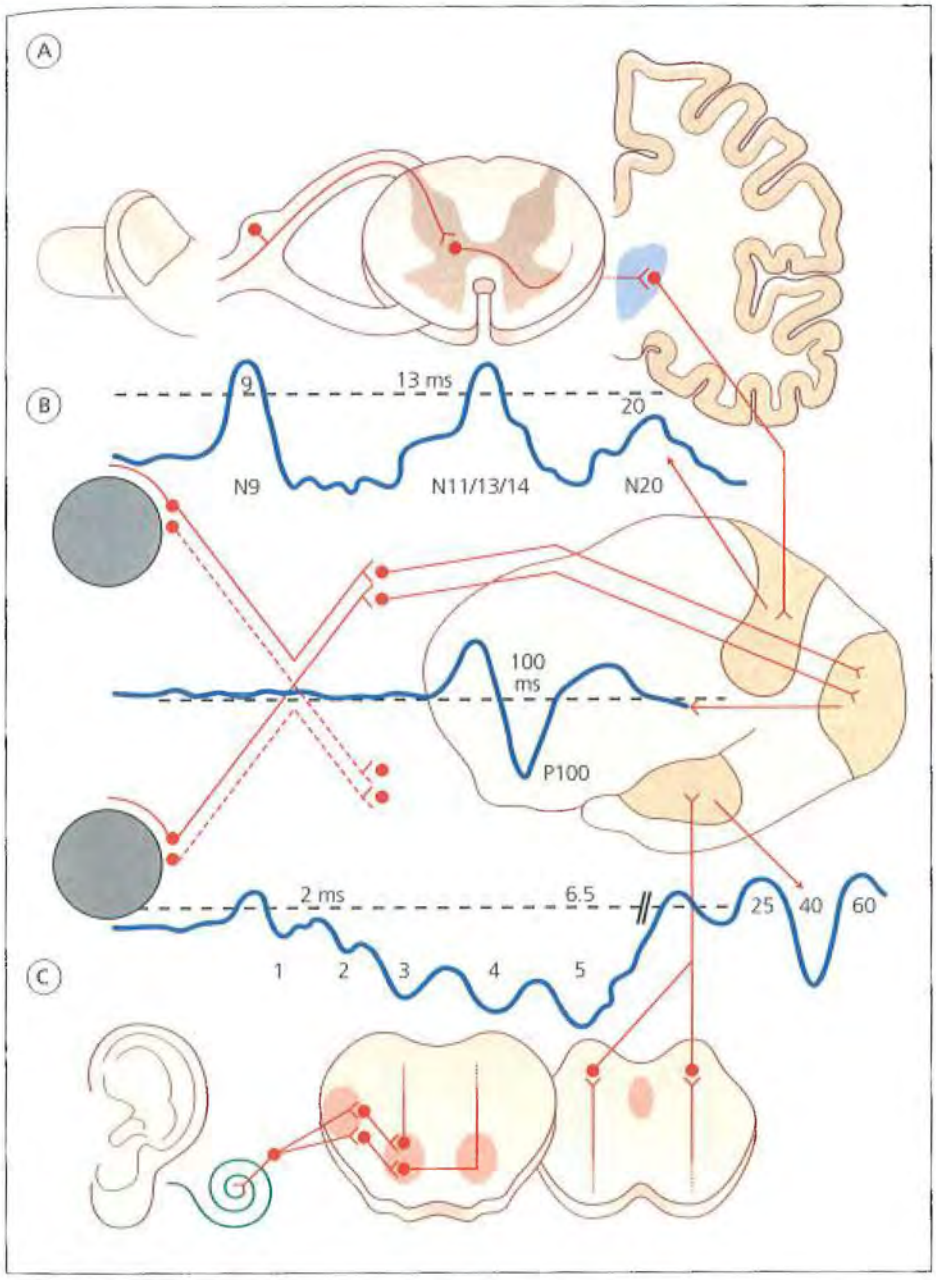


Figure 7.40 Scheme showing the major normal waveforms of the evoked potentials and their sites of origin. (A), Somatosensory, (B) visual and (C) auditory.

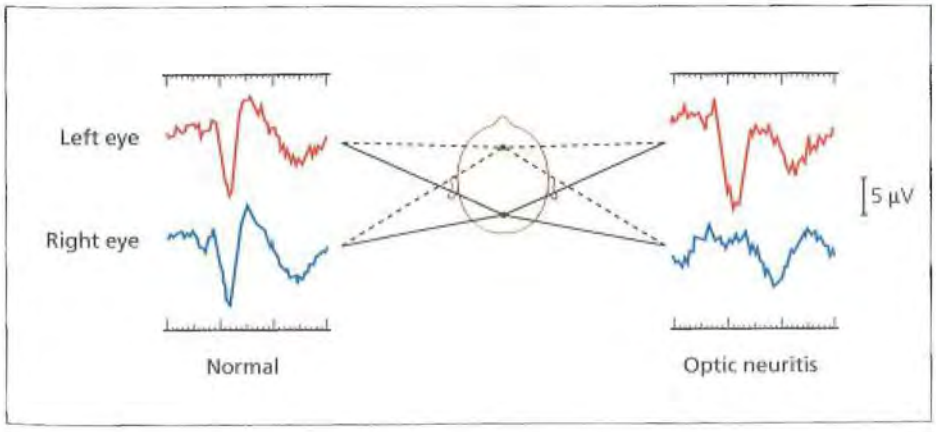


Figure 7.41 Visual evoked potentials to pattern reversal stimulation. On the left are responses from an apparently healthy control and on the right, responses from a patient with acute right optic neuritis. Note the substantial delay in the P100.

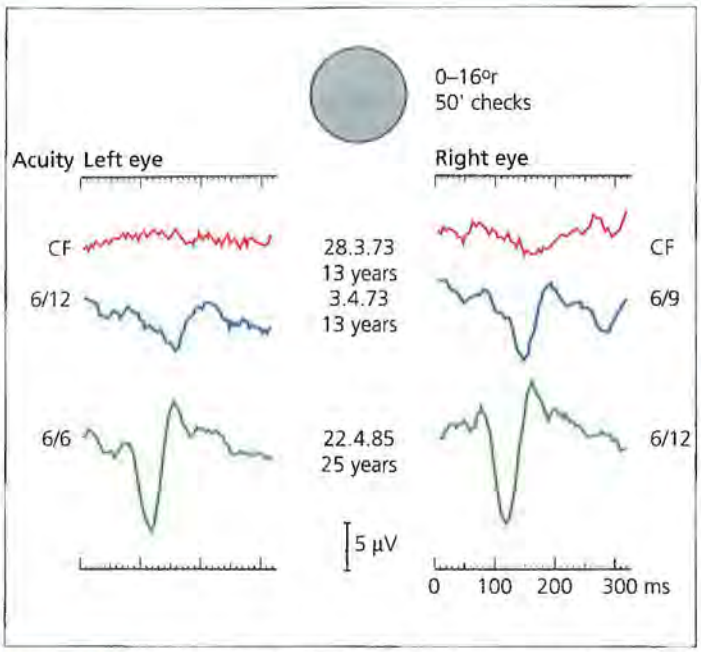


Figure 7.42 Visual evoked potentials to pattern reversal recorded from a girl aged 13 years at presentation, 3 days, 9 days and 12 years after onset of an attack of acute bilateral optic neuritis. Kindly provided by Drs Martin Halliday and Anthony Kriss. Adapted from W.I. McDonald (1986).

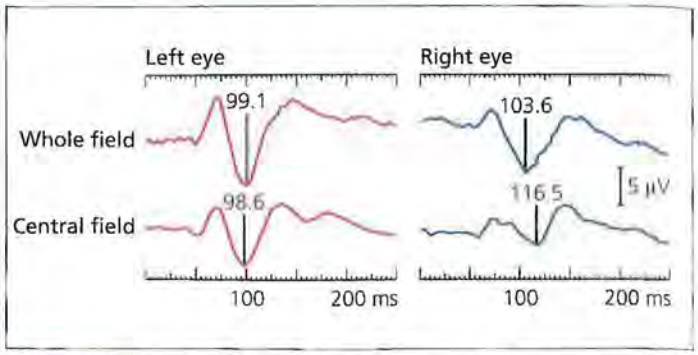


Figure 7.43 Visual evoked potentials to pattern reversal stimulation in a patient with a lesion of the right optic nerve. Top trace. normal response to 'whole' field stimulation; bottom trace. delayed response to stimulation of the central 4°. Kindly provided by Dr Steven Jones.

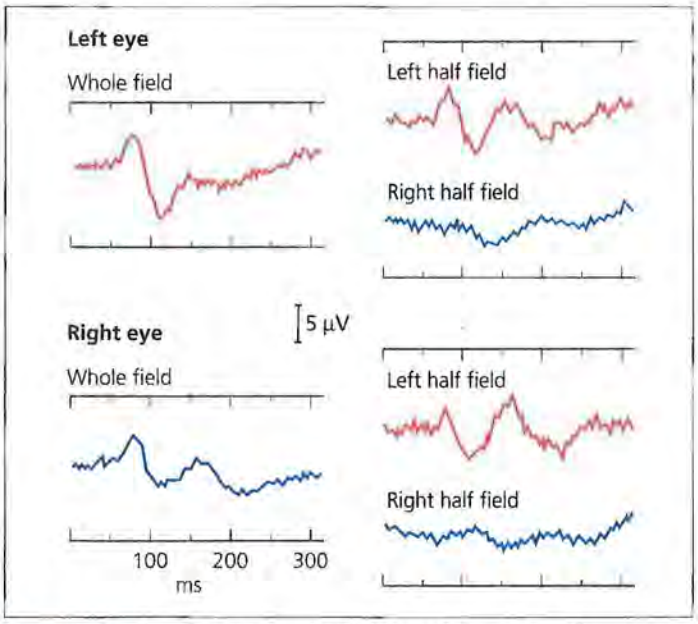


Figure 7.44 Visual evoked potentials to pattern reversal stimulation. Note that the responses evoked from stimulation of the right half fields are delayed compared with those following stimulation of the left half fields. Kindly provided by Dr Steven Jones.

latency of response with increasing years following optic neuritis and proposed that this evolution is compatible with remyelination. After an episode of optic neuritis in childhood, normal latencies are seen in about 50% of patients, perhaps signifying a greater capacity for remyelination in the young (Kriss *et al* 1988; see Chapter 13). Occasionally, the latency from the affected eye remains within normal limits. In these circumstances, the observation of a pathological latency difference between the eyes (>6 ms in our laboratory) may be diagnostically helpful.

When only a small proportion of the fibres subserving central vision is affected, the abnormality may not be detectable within the large response mediated by the normal fibres after full field stimulation. Here, stimulation of the central 4° in isolation may be decisive (Figure 7.43).

Posterior visual pathway lesions

Occasionally, visual symptoms are produced by large lesions involving the optic tract or radiation (Figure 6.24; Plant *et al* 1992; see Chapter 6). Even in the absence of a hemianopia detected by standard clinical methods, delays after stimulating homonymous half fields may be detected to diagnostic advantage (Figure 7.44). Pathologically, demyelinating lesions affect the chiasm in neuromyelitis optica and also in the typical case of multiple sclerosis; however, clinical presentation with a bitemporal hemianopia is exceedingly rare.

Nonorganic visual impairment

The visual evoked potential is often helpful in assessing patients in whom there appears to be a discrepancy in the physical findings suggesting that the abnormality may not be organic in nature. The finding of an evoked potential of normal amplitude, waveform and latency with a visual acuity of 6/24 or less provides strong evidence for nonorganic disturbance. Conversely, when it is uncertain whether any organic abnormality is present and physical examination is normal, the finding of a delay – sometimes detectable only in central field visual evoked potentials – may be invaluable.

Problems of interpretation

In interpreting the results of visual evoked potentials, it is important to be aware that the normal response elicited by stimulation of the paramacular region of the retina in isolation in normal subjects has a latency of approximately 135 ms. Thus, a

central scotoma resulting from any pathological process affecting the retina or optic nerve, whether degenerative or demyelinating, may result in an apparent delay which does not necessarily signify the presence of demyelination; it may instead reflect predominant paramacular stimulation.

Another source of confusion is the distorted waveform that can arise in a variety of conditions often – but not invariably – nondemyelinating in nature. In these circumstances, it may be difficult to identify the P100, and accordingly impossible to determine whether there is a true delay attributable to demyelination.

Finally, although compression of the optic nerve usually produces a visual evoked potential of irregular form without a convincing increase in latency of the P100 (Figure 7.45: Halliday *et al* 1976), it must be remembered that a substantial delay with a well-preserved waveform is simply characteristic of the pathological process of demyelination, however it may be caused. For example, a classical delayed response with a preserved waveform is occasionally seen not in optic neuritis but, rather, arising from compression of the anterior visual pathway (Figures 7.46 and 7.47). This finding is in keeping with the experimental observation of compression-induced focal demyelination in the spinal cord (Holmes 1906) and experimentally in the optic nerve (Clifford-Jones *et al* 1985a; 1985b).

Electroretinogram

Electroretinography is useful as a research tool in the assessment of retinal involvement in demyelinating disease. Various changes have been described at different stages of optic neuritis (Halliday 1993), but they are not of diagnostic help in the investigation of patients suspected of having multiple sclerosis.

Multiple sclerosis

The usefulness of the visual evoked potential in the diagnosis of multiple sclerosis derives from the frequency with which the optic nerve is affected, with or without relevant symptoms, and the usual persistence of the evoked potential abnormality. Overall, this is delayed in approximately 70% of patients suspected of having multiple sclerosis and in up to 90% in some series of patients with clinically definite disease (Halliday 1993).

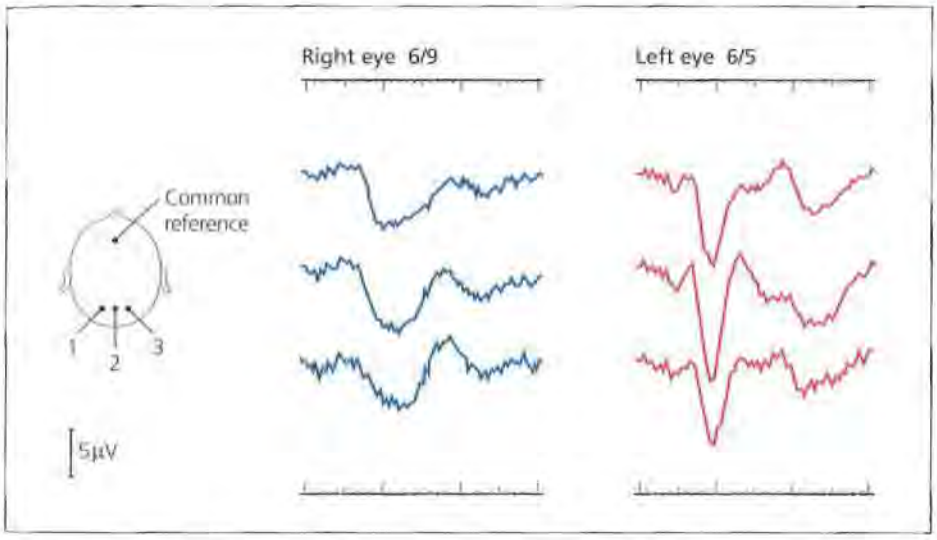


Figure 7.45 Visual evoked potentials after pattern reversal stimulation in a patient with compression of the right intracranial optic nerve by a sphenoid wing meningioma. The waveform is distorted compared with the response from stimulating the left eye. Kindly provided by Dr Martin Halliday.

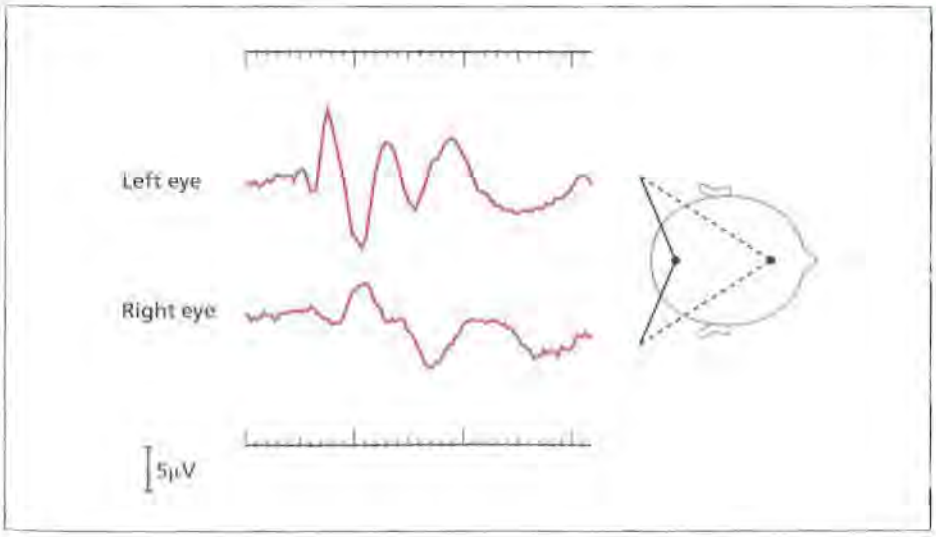


Figure 7.46 Pattern responses from each eye in a patient with a sphenoidal ridge meningioma showing the distortion of normal waveform and the delayed latency of the response from the affected eye. Visual acuity was 6/9 in each eye at the time of the recording. Time scale 10, 50 and 100 ms. From Halliday *et al* (1976) with permission.

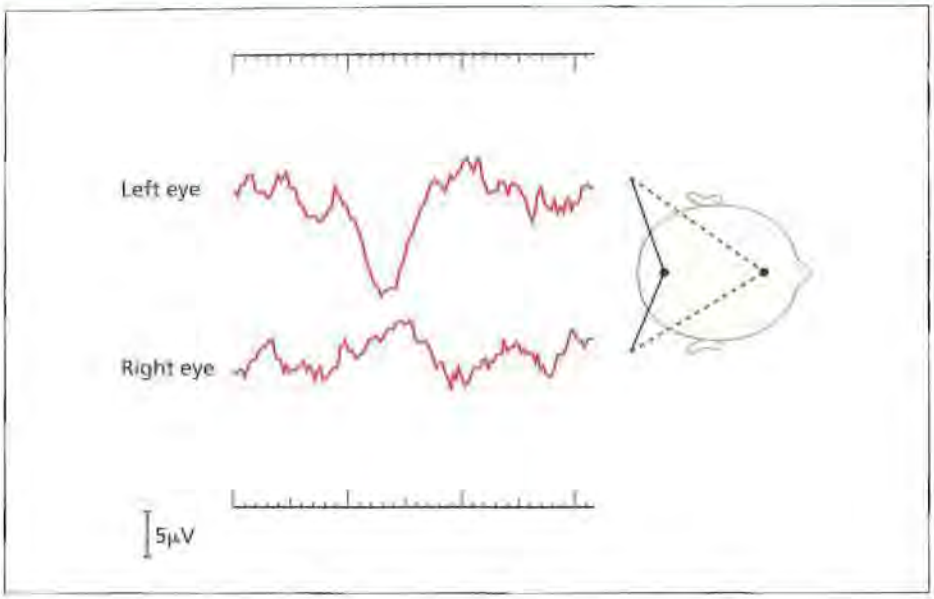


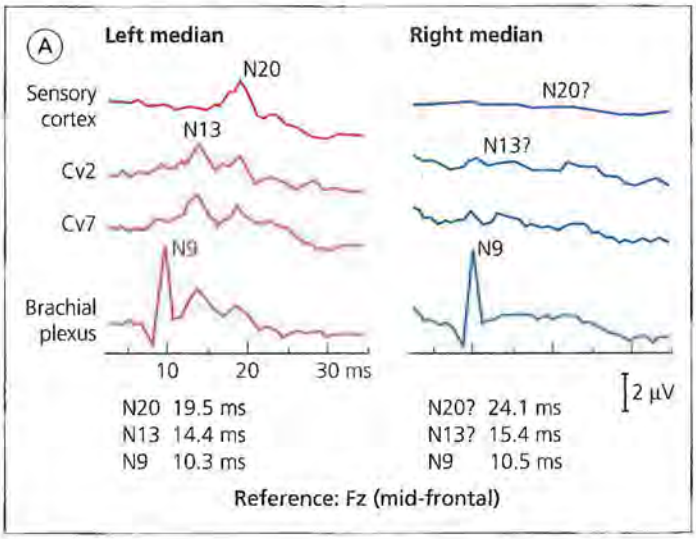
Figure 7.47 Pattern responses from each eye in a patient with pituitary adenoma. VAL 6/6; VAR 6/36. Note the grossly altered waveform of the response from the right eye with loss of the major positive component and a reduction in the overall amplitude. The response from the left eye, which has a reasonably well-preserved waveform, is pathologically delayed. Time scale 10, 50 and 100 ms. From Halliday *et al* (1976) with permission.

As expected, the risk of developing the clinically expressed, disseminated form of multiple sclerosis is increased in those monosymptomatic patients who may present with nonvisual symptoms, if the visual evoked potential is found to be abnormal (see Halliday 1993 for review of the extensive literature). Simply stated, this indicates that a second site is involved but the greater sensitivity of MRI has superseded the visual evoked potential in this setting. Visual evoked potentials are the only electrophysiological diagnostic tests retained in the new diagnostic criteria for multiple sclerosis. A delayed evoked potential does not carry the same status as an emerging MRI lesion in the revised diagnostic criteria (see above; W.I. McDonald *et al* 2001). However, the finding is of particular value when primary progressive multiple sclerosis presents as a progressive myelopathy. In such a context, brain MRI is frequently normal or reveals a paucity of abnormalities but it should be remembered that some genetically determined disorders may be associated with optic pathway and spinal cord involvement, reproducing the clinical and laboratory features of primary progressive multiple sclerosis. Examination of the cerebrospinal fluid achieves special significance in this situation.

In patients presenting with complex clinical pictures in which multiple sclerosis is but one of a number of alternative diagnoses, the finding of a delayed evoked potential is useful in indicating that the pathological process affecting the optic nerve is consistent with demyelination. The cause of the delay is then established from a consideration of the rest of the clinical and investigative picture.

Somatosensory evoked potential

Principles determining the nature of the abnormalities and practical usefulness of the somatosensory evoked potential in the diagnosis of multiple sclerosis are the same as those already discussed with regard to the visual system. The standard method of stimulation is by suprathreshold electrical stimulation of the median or posterior tibial nerves. The response recorded from the scalp over the Rolandic area is dominated by a positive wave at 20 and 40 ms after stimulation of the median



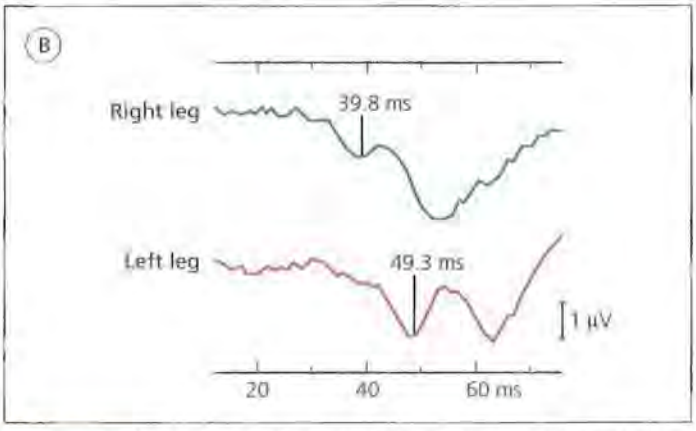


Figure 7.48 Delayed somatosensory evoked potential in clinically definite multiple sclerosis after stimulation of the (A) right median nerve (normal response after stimulation of the left median nerve), (B) left tibial nerve (response following stimulation of the right tibial nerve is of normal latency). Kindly provided by Dr Stephen Jones.

and posterior tibial nerves, respectively (Figure 7.48). Central conduction time is determined by the difference between recordings made over the root entry zones of the cervical and lumbar cord.

As with the visual evoked potential in optic neuritis, the somatosensory response is reduced or absent in the acute phase of demyelinating myelopathy involving the dorsal part of the cord. Given adequate recovery, a delayed response (usually persistent) is found. The choice of the lower or upper limb for stimulation is dictated by clinical needs. When looking for evidence of a cord lesion in an asymptomatic patient, it is best to start with the upper limb somatosensory response both because of the high frequency of plaques in the cervical cord (Oppenheimer 1978) and the greater ease with which this response can be obtained.

The reported frequency of abnormalities in clinically definite multiple sclerosis and in patients without sensory symptoms or signs varies widely. An approximate overall frequency of 80% for clinically definite multiple sclerosis is reasonable, with lower figures for less definite diagnostic categories. Clinically unsuspected lesions may be detected in about 20% of patients being investigated for multiple sclerosis (Small *et al* 1978; Trojaborg and Petersen 1979). Since MRI has now largely replaced somatosensory and auditory evoked potentials as a means of detecting asymptomatic lesions in the diagnosis of multiple sclerosis, the reader is referred to the comprehensive review of Jones (1993) for further details of the variations reported from laboratories investigating different patient groups and using a variety of stimulating and recording techniques.

Auditory evoked potentials

The short latency (≤10 ms) response obtained from scalp electrodes after auditory stimulation by clicks is characterized by five waves, of which I and II originate from the eighth nerve external to the brainstem, wave III from the cochlear nucleus, and IV and V from the region of the superior olivary complex (McPherson and Starr 1993).

In demyelinating disease there is characteristically an increase in latency between I/II and the later waves, the amplitude of which is often reduced (Figure 7.49: Chiappa *et al* 1980; Eisen and Odusote 1980; K. Robinson and Rudge 1977). Abnormalities in the brainstem auditory evoked potentials are rather less frequent than in the visual or somatosensory systems in clinically definite (approximately 50–75%) and suspected (approximately 25%) multiple sclerosis (McPherson and Starr 1993). This investigation is accordingly less useful in the routine diagnostic assessment of patients thought possibly to have multiple sclerosis, especially with the advent of MRI, but can occasionally be of value.

As in the case of the visual evoked potential, end organ damage from whatever cause may interfere with the response as, of course, may conductive deafness, both of which must be excluded before interpreting the results.

In addition to the standard short latency auditory evoked potentials, long latency responses may be elicited by delivering complex harmonic tones. These are more likely to be abnormal than short latency responses in patients with multiple sclerosis (S.J. Jones *et al* 2002), and probably reflect the effects of disseminated central nervous system lesions rather than lesions of the afferent pathway *per se*.

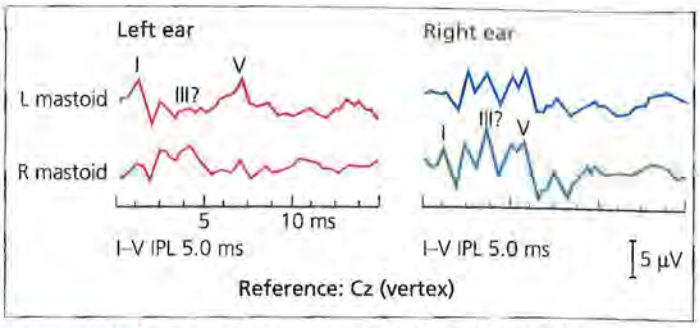


Figure 7.49 Auditory evoked potential in clinically definite multiple sclerosis recorded after click stimulation of each ear. There is an increased latency between waves I and V on left ear stimulation. Kindly provided by Dr Stephen Jones.

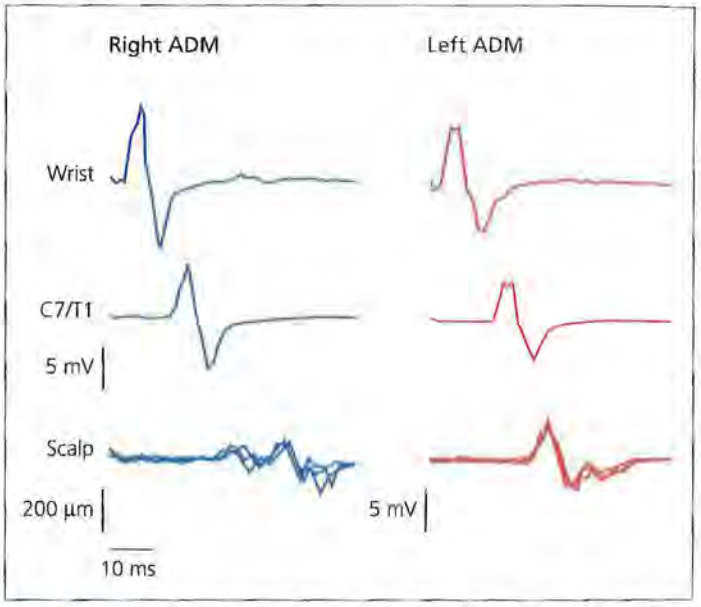


Figure 7.50 Responses recorded from the left and right abductor digiti minimi (ADM) in clinically definite multiple sclerosis after transcranial magnetic stimulation of the contralateral cortex. Note the delay and abnormal waveform in the response from the right (central motor conduction time 9.4 ms) compared with the left (central motor conduction time 6.3 ms) ADM. From Hess *et al* (1986) with permission.

Motor evoked responses

The recording of motor responses to electrical or magnetic cortical stimulation was subsequently added to the repertoire of investigations for the diagnosis of multiple sclerosis. As expected, delays have been demonstrated by both methods (Figure 7.50; Barker *et al* 1986; Cowan *et al* 1984; Hess *et al* 1986; 1987; Ingram *et al* 1987; Mills and Murray 1985; Rossini *et al* 1985). As with afferent evoked potentials, the responses are somewhat variable. This is a consequence of being synaptically mediated. In terms of diagnosis, it must be remembered that there can be a delay in activation of the motor neuron pool in purely degenerative disorders of the cortico-spinal pathway, such as motor neuron disease. Nevertheless, very long delays (of the order of 20 ms) are more likely to result from demyelination

(Thompson *et al* 1987). The diagnostic usefulness of the motor response is limited by the fact that a delay in the response is rarely found in the absence of abnormalities detectable by clinical examination (Hess *et al* 1986; 1987; Murray 1991). Nevertheless, the motor evoked potential has a limited role in the assessment of complex cases. In a study of 19 patients with primary or secondary progressive multiple sclerosis followed up for 1 year, an increasing delay of central motor conduction time was observed in four patients, all of whom also developed new spinal cord lesions on MRI (Kidd *et al* 1998). However, 15 patients in the same study exhibited clinical deterioration indicating that the latter frequently occurs in the absence of a further prolongation of central motor conduction time: the authors took this to mean that clinical progression is more likely the result of increasing axonal loss rather than demyelination.

Other electrophysiological investigations

Although a number of other electrophysiological measures have been applied successfully to detect abnormalities in patients with central nervous system demyelination, none has established a useful role in routine diagnostic practice. In this section, several such techniques are briefly reviewed.

Laser evoked potentials

Laser evoked potentials provide a means for detecting abnormalities in conduction through the spinothalamic tracts. The potentials are elicited by an infrared thulium laser stimulus. The laser beam is directed to produce a painful heat stimulus to the skin of the hand and foot and recordings of the negative and positive evoked potential responses are made at the vertex. An early study revealed absent or delayed responses in 8/12 patients with definite multiple sclerosis (Kakigi *et al* 1992). In a recent analysis, the relative sensitivity of laser evoked potentials was compared with that of standard median and tibial somatosensory evoked potentials in 20 patients who fulfilled standard diagnostic criteria for multiple sclerosis (Spiegel *et al* 2003). Laser evoked potentials were abnormal in 12 (60%) and standard somatosensory recordings were delayed in eight (40%) patients. In seven cases, the abnormalities of spinothalamic function detected using laser evoked potentials were subclinical. Although of interest, because of the apparently greater sensitivity compared with somatosensory evoked potentials, this and other neurophysiological investigations have been largely superseded by MRI as a means for detecting clinically silent lesions.

Ocular microtremor

Using a piezoelectric transducer, abnormalities of ocular microtremor have been studied in patients with multiple sclerosis. In a series of 50 patients, abnormalities were seen in 78%, and were most likely to occur in those with signs of brainstem or cerebellar disease (Bolger *et al* 2000). The frequency of normal (physiological) ocular microtremor was reduced in the multiple sclerosis subjects compared with healthy controls. The investigation has not found a place in diagnosis and would seem unlikely to do so in view of the need to place the monitoring equipment on the sclera.

Vestibular evoked myogenic potentials

This more recently developed neurophysiological technique studies the modulation of tonic electromyographic activity of the sternocleidomastoid muscle in response to a vestibular activation stimulus. It is proposed as a method for detecting brainstem lesions. In a recent investigation of 40 patients with multiple sclerosis, abnormal vestibular evoked myogenic potentials were found in 28 subjects, including four in whom brain MRI was normal (Alpini *et al* 2004). However, in another study of 36 patients with multiple sclerosis, vestibular evoked myogenic evoked potentials were less sensitive than either MRI or visual evoked potentials in detecting abnormalities (Bandini *et al* 2004). Further studies in multiple sclerosis and other disorders will be needed to determine its sensitivity and specificity as a diagnostic tool.

EXAMINATION OF THE CEREBROSPINAL FLUID

Examination of the cerebrospinal fluid obtained at lumbar puncture has had a role in the diagnosis of multiple sclerosis for more than 70 years. Greenfield and Carmichael (1925) showed that a paretic colloidal gold curve in the presence of a negative test for syphilis was characteristic although not, of course, diagnostic for multiple sclerosis. Kabat *et al* (1942) took the next step when they showed that proteins in the cerebrospinal fluid were electrophoretically different from those in serum (see Chapter 1). Further electrophoretic studies followed (Scheid 1944 – see Bauer 1953; Cumings 1953; Felgenhauer 1971), but it was Lowenthal *et al* (1960; Lowenthal 1964) who demonstrated the diagnostic potential of cerebrospinal fluid protein electrophoresis by virtue of bands observed in the gammaglobulin region. Link (1967) showed that these represented immunoglobulin G (IgG); and the group of Dr W.W. Tourtellotte provided evidence that the IgG originated in the lesions of multiple sclerosis (Tourtellotte and Parker 1966; Tourtellotte *et al* 1980). The antigens, however, still await definitive identification. Electrophoresis of the spinal fluid proteins led to a marked increase in sensitivity, but not specificity, in detecting abnormalities. With the advent of other laboratory investigations, in particular MRI, the role of lumbar puncture in the diagnosis of multiple sclerosis is now less important, but it remains of great value in the assessment of complex cases where an important question is whether the disease process is immunologically mediated. In these circumstances, the demonstration of intrathecal IgG synthesis is often crucial in determining the next step in diagnostic assessment, or in supporting a diagnosis of multiple sclerosis when it has been suspected but not definitively established on other grounds.

We discuss the immunological properties of cerebrospinal fluid and the lessons learned for understanding the pathogenesis of multiple sclerosis in Chapter 11. Here, the more pragmatic position is adopted of how the various findings can be used to supplement clinical features in establishing the correct diagnosis of multiple sclerosis in a given case. We consider that examination of the cerebrospinal fluid is particularly valuable in two contexts. In older patients who present some years after first developing symptoms; and in those with a late onset progressive syndrome which may be the result of demyelination, MRI cere-

bral white matter lesions suggestive of multiple sclerosis may be age related and not the result of inflammatory demyelination. The detection of oligoclonal bands is then highly informative. Second, the examination of cerebrospinal fluid has a role in patients with progressive myelopathy at all ages. The revised criteria for the diagnosis of primary progressive multiple sclerosis require the demonstration of oligoclonal bands (McDonald *et al* 2001). To illustrate this point: in the context of cord flattening due to spondylosis on MRI, and with little or no cerebral white matter abnormalities, the question arises of whether the diagnosis is spondylitic myelopathy, primary progressive multiple sclerosis or comorbidity? Often, the presence of oligoclonal bands will tip the balance of probabilities in favour of demyelinating disease and spare the patient unnecessary spinal surgery with a low dividend for clinical improvement (Figure 7.51).

Cerebrospinal fluid examination is also of value in that findings outside the expected range should lead to a careful reassessment of the diagnosis. Now, we discuss the typical profile basing this account on previous summaries, some especially helpful in that they represent consensus reports (Andersson *et al* 1994; Tourtellotte 1985; Tourtellotte *et al* 1988; Whitaker *et al* 1990).

Cell count

It is common to find a modest pleocytosis of 10–20 cells/cm^3 at the time of relapse. That such counts are also seen during clinical remission is not surprising given the five- to 20-fold greater frequency of lesion activity detected by MRI compared with clinical assessments and the chronic persistent inflammatory reaction in the brains of patients in remission. Cell counts of >50 cells/cm^3 are rare and should raise the suspicion of an alternative diagnosis. In acute disseminated encephalomyelitis and transverse myelitis, the cell count may be considerably higher (>100/cm^3) in the acute phase (Miller *et al* 1956). That said, we have occasionally seen counts of up to 100 cells/cm^3 in patients fulfilling standard criteria for the diagnosis of clinically definite multiple sclerosis. Lymphocytes usually make up 90% and polymorphonuclear cells <5% of the differential count. Cytospin preparations also often contain macrophages and the occasional plasma cell.

Total protein

The total protein is normal in about two-thirds of patients, but modestly elevated (0.5–0.7 g/L) in the remainder. Exceptionally, higher levels are seen and, when there is swelling in the spinal cord with an acute lesion, the level may be >1 g/L. Very high levels of protein (>2.5 g/L) may also be found with the rare combination of central and peripheral demyelinating disease fulfilling standard diagnostic criteria for multiple sclerosis and chronic inflammatory demyelinating polyneuropathy (P.K. Thomas *et al* 1987; see Chapter 6). We have seen such a patient with a total spinal fluid protein of 2.6 g/L who developed the additional complication of secondary raised intracranial pressure.

Intrathecal IgG synthesis

Intrathecal IgG synthesis is highly characteristic of multiple sclerosis. The most widely used means for demonstrating this feature is isoelectric focusing of contemporaneous serum and spinal fluid samples, so that the synthesis of IgG specifically in the central compartment can be estimated. In practice, agarose gels are preferred by some laboratories because of a lower false-positive rate but these offer a less sensitive approach (Lunding *et al* 2002). The demonstration of oligoclonal bands in cerebrospinal fluid but not serum (Figure 7.51), or of additional bands in the cerebrospinal fluid despite abnormalities in serum, provides clear evidence for intrathecal synthesis and carries the implication that an immunological process is active in the central nervous system. Using isoelectric focusing, oligoclonal bands are found in >95% of patients with clinically definite disease (Andersson *et al* 1994). Their absence in a patient suspected of

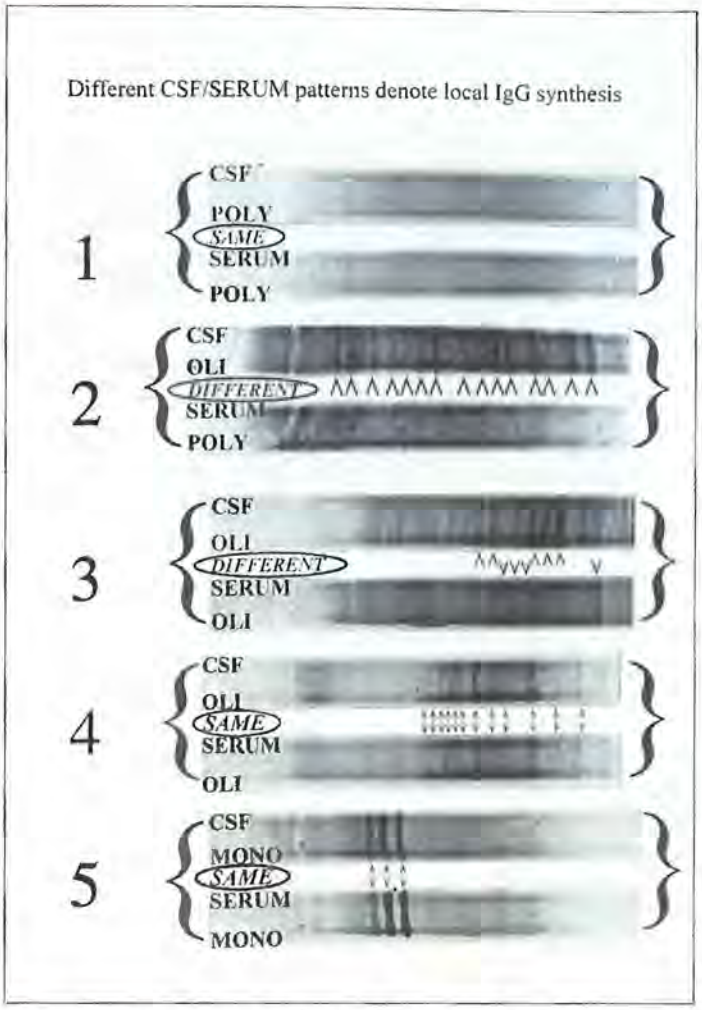


Figure 7.51 Five patterns of isoelectric focusing. Type 1 is a normal pattern from a patient with benign intracranial hypertension. Type 2 is a typical oligoclonal pattern in a patient with clinically definite multiple sclerosis. Type 3 is a 'greater than' pattern, also in a patient with clinically definite multiple sclerosis where there are more bands in cerebrospinal fluid than in the corresponding serum sample. Type 4 is a mirror pattern in which the same bands found in the systemic circulation are passively transferred into the spinal fluid, in this case from a patient with the Guillain–Barré syndrome. Type 5 is a monoclonal paraprotein in serum transferred passively into the spinal fluid in a patient with IgG paraprotein neuropathy. POLY = polyclonal; OLI = oligoclonal; MONO = monoclonal. Cathode is on the right. From Andersson *et al* (1994) with permission.

having multiple sclerosis should lead to a careful reassessment of evidence for the diagnosis (Zeman *et al* 1996). The presence of identical bands in serum and cerebrospinal fluid indicates a systemic immune response with passive transfer of immunoglobulin from serum, and is of no diagnostic value. It should also be noted that the frequency of oligoclonal bands in the cerebrospinal fluid of Oriental patients with clinically definite multiple sclerosis is lower (approximately 33%: Y.L. Yu *et al* 1989) than in patients of European origin (>90%; McLean *et al* 1990). It is unclear whether this relates to the higher frequency of optico-spinal presentation reported in Oriental populations (see Chapters 5 and 6).

Oligoclonal bands are sometimes absent at or near the clinical onset of multiple sclerosis, but emerge after follow-up and repeat lumbar puncture. Serial analysis of the cerebrospinal fluid has shown that once present, oligoclonal bands persist in individuals with multiple sclerosis. Disappearance, as may be seen in acute disseminated encephalomyelitis (Kesselring *et al* 1990), makes the diagnosis of multiple sclerosis highly unlikely. The presence of oligoclonal bands in patients with optic neuritis and other clinically isolated syndromes is associated with an increased likelihood of conversion to clinically definite multiple sclerosis in the next 5 years (see Chapter 6).

Several other approaches have been taken to demonstrate intrathecal IgG synthesis. The Link index is the ratio of IgG in cerebrospinal fluid and serum divided by the ratio of albumin in spinal fluid and serum. It correlates with the results of cerebrospinal fluid electrophoresis or isoelectric focusing but is rather less sensitive than these qualitative methods (Andersson *et al* 1994). Quantitative methods have also been developed for intrathecal IgG production (Tourtellotte 1985), but they are technically difficult and are more relevant to research than routine diagnosis (Andersson *et al* 1994).

It must be emphasized again that, as in the case for MRI and evoked potentials, the demonstration of oligoclonal bands present selectively in cerebrospinal fluid is not specific for multiple sclerosis. It tells the physician that there is an intrathecal immunological abnormality. Other clinical and investigative data provide the evidence from which the cause may be determined. Intrathecal IgG synthesis is seen in several other immunological disorders, in acute and chronic inflammation or infection of the brain and meninges, and in the paraneoplastic syndromes (McLean *et al* 1990; see Chapter 8). Although it is claimed that neurosarcoidosis may be associated with oligoclonal bands in the cerebrospinal fluid (McLean *et al* 1990; Zajicek *et al* 1998), a current expert view suggests that such bands may not be found in histologically confirmed disease (Ed Thompson, personal communication). Further study of this difficult topic is clearly needed. Although the number of possible causes for increased intrathecal IgG synthesis is large, it is true to say that amongst individuals of northern European origin living in temperate climates, multiple sclerosis is outstandingly the commonest cause of intrathecal IgG synthesis.

Cerebrospinal fluid oligoclonal IgA and IgM bands also occur in multiple sclerosis (Leary *et al* 2002; Vilar *et al* 2003). A recent report suggests that the presence of cerebrospinal fluid oligoclonal IgM may be associated with a poor long-term prognosis (Villar *et al* 2003). However, this study was small and only 11/29 individuals had IgM bands. A later report from the same investigators reported more relapses and disability in 15 patients who had oligoclonal IgM against myelin lipids when compared with 33 patients who lacked such bands (Villar *et al* 2005). Further work is needed to investigate this potential prognostic marker.

Other investigations using blood and cerebrospinal fluid

Because the composition of cerebrospinal fluid reflects aspects of what is happening in the central nervous system parenchyma, several procedures have been developed to analyse many of its normal and pathological constituents, including those that reflect spillover of processes also active in the systemic circulation or specifically located in the central nervous system. Peripheral blood markers of disease activity are more likely to be dominated by systemic immunological or inflammatory events unrelated to events germane to the central nervous system disorder. Potential markers of disease have included measurements of lymphocyte subpopulations (Navikas *et al* 1996a; 1996b), production of cytokines (Peter *et al* 1991), endothelial cell markers (Dore-Duffy *et al* 1995; Minagar *et al* 2001), cholesterol (Giubilei *et al* 2002) and myelin breakdown products, which are also detectable in urine (Whitaker *et al* 1993; 1994). Myelin breakdown products, of course, are detected whenever there is myelin destruction whether this results from primary demyelination or is secondary to axonal degeneration induced by infarction, trauma or chronic degenerative disorders. These procedures do not currently have a role in routine diagnostic assessment of the individual patient. Similarly, measurements of putative biochemical markers of glial proliferation or axonal loss in the cerebrospinal fluid – such as S110b protein, 14-3-3 protein and nonphosphorylated neurofilaments – are likely to demonstrate abnormalities in a number of neurodegenerative and neuroinflammatory disorders in which gliosis and axonal loss occur (Irani and Kerr 2000; De Séze *et al* 2002).

Petzold and colleagues (2002) investigated biomarkers for glial responses in the cerebrospinal fluid of 51 patients with multiple sclerosis. Patients with severe locomotor disability exhibited higher levels of cerebrospinal fluid glial fibrillary acidic protein when compared with less disabled patients and controls. Levels of S100b tended to be higher in relapsing–remitting subjects than in those with secondary or primary progressive disease and post-mortem examination revealed that S100b was higher in histopathologically acute lesions. The authors suggest that there are different patterns of glial activation according to disease course and disability.

Axonal markers may be of more relevance for monitoring disease progression (Martinez-Yelamos *et al* 2001) since axonal loss is the major substrate of irreversible disability in multiple sclerosis. Phosphorylated forms of neurofilament are principal components of the axoskeleton released during axonal injury. In a recent study, two neurofilament heavy chain phosphoforms were analysed from the cerebrospinal fluid of 34 patients with multiple sclerosis and 318 noninflammatory neurological controls (Petzold *et al* 2005). Measures were taken at baseline and after 3 years. An increase in the NfH^{S135} was seen in 59% of patients with primary or secondary progressive multiple sclerosis but in only 14% with relapsing–remitting disease. The level of $NfHS^{135}$ was also moderately correlated with disability. These

results support the notion that progressive axonal loss underpins increasing disability and suggest that the cerebrospinal fluid level of NfH^{SI35} may be a prognostic marker. Confirmation of these findings in another study is needed.

Recent interest has been shown in the measurement of serum anti-myelin antibodies. While these are present in subjects with multiple sclerosis, there has not been a convincing demonstration of their specificity or sensitivity as a diagnostic tool. A recent study by Berger *et al* (2003) investigated 103 patients with clinically isolated syndromes of the type seen in multiple sclerosis. The subjects were pre-selected by requiring the presence of disseminated white matter lesions on brain T_2-weighted MRI that fulfilled the Fazekas criteria (Fazekas *et al* 1988), accompanied by the presence of cerebrospinal fluid oligoclonal bands. At presentation, 22 had antibodies to both myelin basic protein and myelin oligodendrocyte glycoprotein, 42 had antibodies to myelin oligodendrocyte glycoprotein alone, and 39 did not have antibodies to either of these myelin antigens. During follow-up, further relapses allowing a diagnosis of clinically definite multiple sclerosis occurred in 21/22 (95%) who were positive for both antibodies, 35/42 (83%) who were positive for anti-myelin oligodendrocyte glycoprotein, but in only 9/39 (23%) who were negative for both antibodies. It should be noted that this study cohort was biased by the application of entry criteria that ensured a high *a priori* likelihood of having multiple sclerosis. The most one can infer is that, in those clinically isolated syndrome patients who – from the presence of characteristic multifocal MRI white matter lesions – have a strong probability of developing multiple sclerosis, the absence of anti-myelin antibodies may identify a subgroup in whom the risk is somewhat lower. The remarkable finding of this single study needs to be confirmed in other laboratories and in a broader cohort of unselected patients with clinically isolated syndromes. The subsequent reports that patients with multiple sclerosis and healthy controls have a similar proportion of anti-myelin oligodendrocyte glycoprotein IgG and IgM (Lampasong *et al* 2004) and that anti-myelin antibodies do not correlate with either MRI abnormalities or development of early multiple sclerosis in a cohort of patients with isolated optic neuritis (Lim *et al* 2005) raise doubts whether these laboratory findings will prove to have a sustainable diagnostic value.

More recently, Lennon *et al* (2004) have described a serum marker for the subgroup of patients in whom the clinical phenotype is dominated by optico-spinal multiple sclerosis or neuromyelitis optica. The investigators in this study used indirect immunofluorescence with a composite substrate of mouse tissues to identify a distinctive pattern of IgG staining of central nervous system microvessels, pia, subpia and Virchow–Robin spaces. They called this antibody NMO-IgG and found that it was present in 33/45 (73%) North American patients who had a definite diagnosis of neuromyelitis optica made on the basis of having clinical involvement confined to the optic nerves and spinal cord in association with various combinations of a normal brain MRI scan at first presentation, a spinal cord lesion extending over more than three vertebral segments on MRI investigation, and a cerebrospinal fluid pleocytosis greater than 50×10^6 white cells per litre. The NMO-IgG autoantibody was also identified in 6/11 (55%) Japanese patients with the optico-spinal form of multiple sclerosis and in 16/35 (46%) North American patients who were considered to be at high risk of neuromyelitis optica in that they had either monophasic or recurrent transverse myelitis with a longitudinally extensive cord lesion or recurrent optic neuritis. In contrast, NMO-IgG was detected in only 2/22 (9%) North American patients with multiple sclerosis in whom the presentation was with optic nerve or spinal cord involvement and in none of 24 patients with classical multiple sclerosis (19 North American and 5 Japanese) who were included as a pathological control group. This study suggests a potentially important role for NMO-IgG testing in the differential diagnosis of inflammatory myelopathies and optic neuropathies – independent confirmation of the findings from other laboratories is awaited.

A STRATEGY FOR THE INVESTIGATION OF DEMYELINATING DISEASE

We conclude with a scheme that we consider to represent a compromise between economy, precision and convenience – both for the patient and neurologist – in investigating the individual suspected of having demyelinating disease. It embodies the principles of the available methods and our clinical experience in their application.

A key aspect in selecting which investigations to perform is their sensitivity to detect relevant abnormalities, and hence their likelihood of providing positive diagnostic information. It is therefore important to note that MRI is more likely than evoked potentials to demonstrate dissemination in space, and that there is a high probability of detecting oligoclonal bands in cerebrospinal fluid in established multiple sclerosis. The study of Beer *et al* (1995) highlights the relative sensitivity of paraclinical tests in their diagnostic classification of 189 consecutive patients referred for suspected multiple sclerosis. At discharge from hospital, 142 individuals received a diagnosis of multiple sclerosis based on the Poser criteria and 47 were classified as not having multiple sclerosis. The authors found that, when taken as single tests, imaging had the greatest reclassification sensitivity (60%), followed by examination of the cerebrospinal fluid (31%), and then visual (28%), motor (19%) and somatosensory evoked (12%) potentials. It was noted that MRI had a lower specificity than the other investigations, emphasizing the importance of applying the more specific rules to define the nature of the required imaging abnormalities, as embodied in the recent diagnostic criteria (W.I. McDonald *et al* 2001). It should be stressed again that no imaging, cerebrospinal fluid or evoked potential abnormality is 100% specific for multiple sclerosis. Undue or exclusive reliance on any of the paraclinical investigations invites misdiagnosis.

In clinical practice, patients present with symptoms attributable to demyelination of the central nervous system in one of three categories:

- individuals with unequivocal relapsing–remitting episodes, originating from separate sites within the central nervous system, in whom demyelination is the most likely pathophysiological explanation for each event (clinically definite or probable multiple sclerosis)
- individuals with a recent clinically isolated episode typical of demyelination, with or without a suspicious past history

- individuals with slowly progressive neurological symptoms which might be due to demyelination.

Clinically definite multiple sclerosis

The patient with episodes disseminated in time, each of which can be attributed to demyelination, requires no investigation prior to establishing the diagnosis of clinically definite multiple sclerosis if presentation occurs between the ages of 20 and 50 years, separate anatomical sites within the central nervous system have necessarily been affected on different occasions, and the clinical phenotype is typical for multiple sclerosis. Nevertheless, it can nowadays be considered as normal practice to confirm the clinically definite diagnosis by demonstrating the presence of characteristic abnormalities in brain MRI. These are expected in >95% of such individuals.

When the criteria for clinically definite multiple sclerosis are not met – perhaps the patient has a typical history of relapsing and remitting symptoms but on examination has signs of only one central nervous system lesion – the first and most appropriate investigation is brain MRI. If this demonstrates typical abnormalities, no further investigation is necessary but some neurologists nevertheless advise cerebrospinal fluid examination to demonstrate intrathecal inflammation. Some still perform multimodal evoked potentials if imaging and spinal fluid are both normal, since multiple sclerosis very occasionally occurs in the absence of MRI or cerebrospinal fluid abnormalities. However, the main priority in such cases is to consider and exclude conditions that can mimic multiple sclerosis, and to establish that there is an organic neurological disease.

It is not uncommon to encounter patients giving a history compatible with, but not strongly suggestive of, multiple sclerosis in whom there are no abnormalities on examination. In this context, the first step is to determine whether any organic abnormality is present. Our approach is to begin with MRI of the brain and, if this is normal, the spinal cord provides complementary evidence excluding a structural abnormality. An important caveat to bear in mind in this context is the nonspecificity of several small subcortical white matter lesions on brain MRI. These are a not uncommon incidental finding in middle-aged adults and may even occur in younger people. Many neurologists will be familiar with radiological reports that have inappropriately suggested demyelination leading to worried and frightened individuals being given an incorrect diagnosis of multiple sclerosis entirely out of clinical context. Conversely, small, well-defined, intrinsic spinal cord lesions do not occur with aging or small vessel disease *per se* and provide more specific evidence for demyelination (Bot *et al* 2002). Examination of visual, auditory and somatosensory evoked potentials can also be useful. Significant delay provides evidence for the pathological process of demyelination although, as emphasized above, this is not specific for multiple sclerosis. Rarely, it may be appropriate to examine the spinal fluid for evidence of inflammation but, when symptoms are thought not to be organic, lumbar puncture is best avoided. Every experienced clinician will recall patients in whom the procedure added little but was later perceived to have been complicated – usually 'causing' intractable backache – and sustaining a variety of nonorganic complaints. Although some of us have occasionally made the diagnosis of multiple sclerosis in individuals whose symptoms and signs did not match the criteria for clinically definite multiple sclerosis, and in whom all three categories of investigation were normal, this would have to be seen as an exceptional situation. In general the diagnosis should be considered less likely as each investigation proves negative.

Other structural lesions, such as meningioma, can present with relapsing symptoms and it is for this reason that investigation is essential, even in the context of a relapsing history, if the previous events have not involved separate sites in the central nervous system. Even when the history does implicate different parts of the nervous system, errors can occasionally arise from the co-existence of more than one disease. It is for this reason that the individual past episodes need to be evaluated carefully before deciding that investigation is unnecessary, even in the patient with a relapsing history.

The age limits of 20–50 years are conservative and a significant number of patients with multiple sclerosis present in childhood or later than the sixth decade. However, outside this age band, the probability of an alternative diagnosis increases and the threshold for investigation of disorders that may mimic multiple sclerosis falls. The diagnosis of multiple sclerosis should always be more carefully considered in ethnic groups in whom it is known to be less common (see Chapter 3).

The isolated demyelinating lesion

The decision to investigate patients with an isolated episode of demyelination and a past history of neurological symptoms depends entirely on interpretation of the previous event. If, in retrospect, this can also be attributed with confidence to demyelination, management is the same as for patients with disease disseminated in time. If the previous episode is of doubtful significance, investigation follows the protocol for patients with a first episode of demyelination. Much therefore depends on interpretation of the past history; making the distinction between significant previous episodes and those that can safely be ignored requires clinical experience. Symptoms that are likely to be relevant in making the diagnosis of multiple sclerosis in the patient with a recent episode of demyelination, but which may not have assumed significance at the time, include unilateral blurring of vision, numbness in an anatomical distribution (such as the lower limbs and trunk as far as the waist) or Lhermitte's symptom, double vision and inability to use a limb, especially if these complaints have been present for several days or weeks. Symptoms from the past history, often mentioned by patients but usually turning out not to be important, include any neurological events lasting <24 hours, patchy numbness relieved by change in posture, giddiness, encephalitis or meningitis, bladder symptoms on straining, psychiatric symptomatology and epilepsy.

The approach to investigation and diagnosis of patients who present with a clinically isolated syndrome typical of demyelination (for example, unilateral optic neuritis, internuclear ophthalmoplegia or partial myelitis) should take account of the recently published new diagnostic criteria for multiple sclerosis (W.I. McDonald *et al* 2001). For the first time, these make it possible to diagnose multiple sclerosis after a single clinical episode using paraclinical investigations to establish dissemination in space and time. As discussed above, since the criteria have

been published, further experience has been reported of their application in the context for which they were partially designed – the patient with a clinically isolated syndrome – and, in particular, their ability to predict the development of clinically definite multiple sclerosis. The MRI criteria for dissemination in space and time have a high specificity and positive predictive value for clinically definite multiple sclerosis (Dalton *et al* 2002a; Tintoré *et al* 2003). However, sensitivity of the dissemination in time criteria is low after 3 months follow-up because, at this time point, the criteria require there to be a gadolinium enhancing lesion (Dalton *et al* 2002a). Substitution of a new T_2 lesion for a gadolinium enhancing lesion at this stage increases sensitivity without losing specificity (Dalton *et al* 2003a). Because of the overall robustness of these criteria, we think it is now appropriate to discuss the possibility of multiple sclerosis with young adults who present with clinically isolated syndromes and to offer further investigations designed to refine the probability or actually establish the diagnosis of multiple sclerosis.

The strategy for investigation of clinically isolated syndromes should always include a consideration of other potential diagnoses, often starting with some simple blood tests, for example towards the exclusion of systemic lupus erythematosus, neurosyphilis and Lyme disease. The choice of more specific investigations will depend on the anatomical region involved clinically. In the case of brainstem syndromes, brain MRI is mandatory, as is spinal MRI in patients presenting with isolated spinal cord syndromes. In clinically isolated optic neuritis, there should always be a specialist ophthalmology review, bearing in mind that some conditions – neuroretinitis and central serous retinopathy – may be otherwise impossible to distinguish from optic neuritis. Imaging is not usually required for the diagnosis of optic neuritis, and the decision whether to perform brain MRI is based on the potential for predicting or diagnosing multiple sclerosis. We approach this issue by first explaining that for about 50–60% of people with optic neuritis, the cause is multiple sclerosis. We discuss something of the nature of multiple sclerosis, emphasize its potential to be benign, and then offer to perform brain MRI to refine the prognosis explaining that an abnormal scan implies a 60–80% likelihood of having multiple sclerosis whereas a normal scan reduces that probability to around 20%. In those who opt for investigation, we arrange a T_2 and gadolinium enhanced scan and follow the patient up promptly. If the scan has been performed >3 months after the attack and fulfils the McDonald criteria for dissemination in space and time, multiple sclerosis is diagnosed. If the scan is abnormal but the criteria for multiple sclerosis are not fulfilled, we suggest a repeat T_2-weighted scan between 3 and 6 months after the original study, as this offers the best prospect of establishing MRI evidence for dissemination in space and time (Dalton *et al* 2003a). Not all patients wish to undergo initial or repeat scanning and it is clearly important to respect their wishes at each stage. We also do not recommend repeat scanning beyond these two initial studies since it becomes increasingly likely that the disease will declare itself clinically as much as by MRI in the longer term.

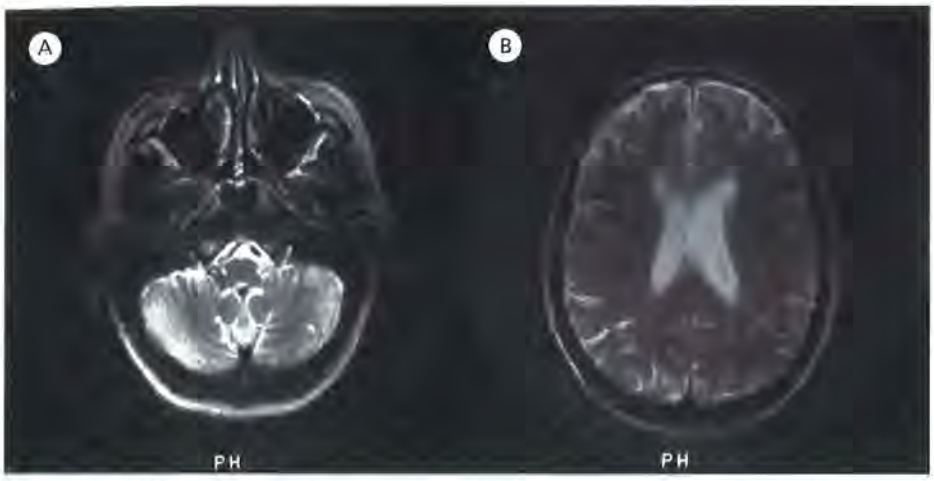
Within the McDonald criteria, the combination of cerebrospinal fluid evidence for oligoclonal bands along with two T_2 brain lesions is sufficient to constitute evidence for dissemination in space. Detection of oligoclonal bands in a patient with a clinically isolated syndrome in whom there is incomplete or absent imaging evidence for multiple sclerosis can be useful in suggesting the likelihood of inflammatory demyelination. Whichever criteria for dissemination in space are used (MRI alone or MRI combined with examination of cerebrospinal fluid) an essential requirement for diagnosing multiple sclerosis using the McDonald criteria is the evidence on MRI of new lesions at least 3 months after the clinical attack. This requirement not only improves specificity of the criteria for developing clinically definite multiple sclerosis (Dalton *et al* 2002a; Tintore *et al* 2003) but also helps to avoid misdiagnosing cases of acute disseminated encephalomyelitis as multiple sclerosis. It should, however, be noted that acute disseminated encephalomyelitis is uncommon in the adult age group, and rarely presents as one of the clinically isolated syndromes typically ushering in the clinical course of multiple sclerosis. If doubt exists in distinguishing the two conditions, serial MRI and cerebrospinal fluid examination may assist: in acute disseminated encephalomyelitis, it would be unexpected for new lesions to develop over a period longer than several weeks and, perhaps, for oligoclonal bands either not to be present at all or – unlike multiple sclerosis – to disappear with follow-up.

This discussion of our approach to investigating patients with optic neuritis and other clinically isolated syndromes addresses only the issue of diagnosing multiple sclerosis. A separate but highly relevant issue arises when there is consideration given to commencing early disease-modifying treatment. Based on evidence that interferon-β delays the time from first attack to development of clinically definite multiple sclerosis in those with abnormal MRI (Comi *et al* 2001a; Jacobs *et al* 2000), it is the practice of some neurologists to initiate therapy after one episode. In these circumstances, MRI abnormalities are taken into account in deciding whom to treat. In countries where guidelines for disease-modifying treatments in multiple sclerosis require that there have been two relapses in the previous 2 years, the issues dictating investigation after single clinical episodes are those relating to diagnosis.

The progressive syndrome

Investigation is mandatory when there is uncertainty about the nature of the presenting episode, and in all patients with slowly progressive symptoms originating from a single anatomical site. The first priority is to assess the affected part radiologically. Formerly, a common error was to restrict examination by contrast myelography to the level at which clinical symptoms were perceived to have arisen, failing to recognize that, in the context of spinal cord disease, motor signs discriminate poorly between different sites of involvement and that sensory levels are necessarily displaced several segments from the affected level because of the lamination of fibres in ascending sensory pathways. This strategic error is less likely with the advent of MRI and the whole of the spinal cord can be readily imaged in a single field of view using phased array receiver coils. In all patients presenting with progressive spastic paraplegia, spinal MRI is mandatory unless it is contraindicated, in which case myelography will still be required.

Even if spinal cord imaging shows an appropriately placed structural abnormality, the clinician still needs to decide on its



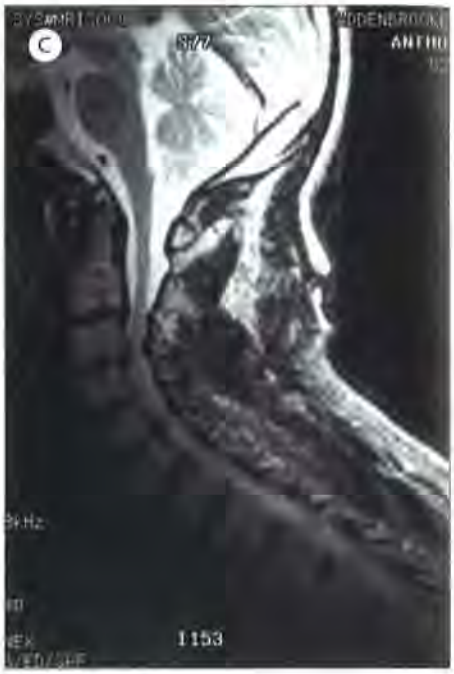


Figure 7.52 (A) T_2-weighted image showing few high signal abnormalities in the cerebellum of a patient aged 65 years with a progressive cerebellar syndrome, oligoclonal bands and delayed visual evoked potentials. (B) Periventricular abnormalities in the same patient. (C) Cord flattening as a result of spondylitis in a patient with a primary progressive spinal cord syndrome, oligoclonal bands and delayed visual evoked potentials.

significance. A large extradural tumour or intrinsic swelling arising from astrocytoma or ependymoma can reasonably be taken to account for the presenting symptoms and be managed by neurosurgical and neuro-oncological colleagues in the appropriate manner. However, other structural abnormalities may be detected, such as disc herniation with narrowing of the cervical canal and slight cord compression, which are not necessarily significant – the presenting symptoms and signs of demyelination happening to arise (coincidentally) at a site of minor but insignificant structural damage. Under these circumstances, and always when imaging shows no structural lesion, it is necessary to carry out MRI of the head, seeking to demonstrate white matter abnormalities indicative of multifocal inflammatory brain disease. If cerebral MRI precedes radiological investigation of the clinically affected part, the possibility arises that white matter abnormalities will be demonstrated and the diagnosis of multiple sclerosis made, even when there is a significant coexisting local lesion.

Since it is now known that nonspecific white matter abnormalities almost never occur spontaneously in the spinal cord in otherwise normal individuals, their detection can be taken as evidence for the process of demyelination, although on a single scan this will not distinguish between a monophasic illness and multiple sclerosis. In the context of a progressive spastic paraplegia of at least 1 year's duration, the presence of two or more discrete spinal cord lesions of a type characteristic of demyelination can be used to support a diagnosis of primary progressive multiple sclerosis (W.I. McDonald *et al* 2001; A.J. Thompson *et al* 2000). A combination of one cord lesion and between four and eight brain lesions may also be used to support a diagnosis of primary progressive multiple sclerosis, as may nine or more brain lesions alone – providing that the brain lesions also appear characteristic for demyelination and cord imaging has excluded any other pathological process. Without evidence for cerebrospinal fluid oligoclonal bands to accompany these imaging findings, the most recent diagnostic criteria recommend that the diagnosis of primary progressive multiple sclerosis should be regarded as probable; when bands are present, it may be classified as definite (A.J. Thompson *et al* 2000).

Analysis of cerebrospinal fluid may also resolve difficult diagnostic situations when imaging both the affected part and the cerebrum fails to provide sufficient information for establishing the diagnosis (Figure 7.52). Evoked potentials may also be delayed in disorders that present with progressive disease at a single site in older patients, and hence run the risk of confusion with multiple sclerosis. In these situations, the demonstration of oligoclonal bands favours the diagnosis of inflammatory brain disease rather than late onset genetically determined or degenerative conditions and can resolve an otherwise diagnostically difficult problem.

Where neuroradiological investigation and spinal fluid analysis exclude a structural abnormality but fail to provide evidence sufficient for the diagnosis of multiple sclerosis, it is appropriate to review the patient after several months and be prepared to repeat all the investigations. Every clinician experienced in the management of neurological disease will have encountered patients in whom competent investigation at presentation failed to detect a structural lesion that subsequently became clinically and radiologically apparent. Likewise, the laboratory evidence for demyelination may only emerge during follow-up.

UPDATING THE MCDONALD DIAGNOSTIC CRITERIA AND THE PROSPECT OF FUTURE REVISIONS

It is inevitable that as further experience is reported in the application of existing diagnostic investigations, and as new diagnostic techniques emerge, internationally accepted criteria for the diagnosis of multiple sclerosis will periodically be amended and updated. Indeed, an International Panel was convened in March 2005 to review the widely accepted criteria that were

developed by another panel 4 years earlier (W.I. McDonald *et al* 2001). In a prior review article, three members of the new International Panel had considered the performance of these 2001 criteria based on reports that had emerged in the 3 years subsequent to their publication (Polman *et al* 2005b). While a generally favourable performance had been evident, potential areas for modification and improvement were identified. These included:

- more specific definitions for clinical dissemination in space
- less stringent criteria for MRI dissemination in space
- allowing a new T_2 lesion as early evidence for dissemination in time in patients with single clinical episodes
- greater integration of spinal cord MRI findings
- no longer a requirement for the presence of cerebrospinal oligoclonal bands to diagnose primary progressive multiple sclerosis.

The revised criteria developed by the new Panel were published late in 2005 (Polman *et al* 2005c). They partly address the issues anticipated above and also reaffirm the 2001 criteria in taking the view that multiple sclerosis should not be diagnosed in the absence of any objective clinical evidence for abnormality. The main areas of revision – summarized in Table 7.5 – are in the MRI criteria for dissemination in space and time (for application in patients who present with a relapse onset syndrome) and in the diagnostic criteria for patients with a slowly progressive syndrome.

Although some of the revisions are logical and expected, ambiguities and uncertainties remain:

- Why does the interval for fulfilling MRI dissemination in time differ for a new T_2 lesion (> 30 days) and a gadolinium-enhancing lesion (≥ 3 months)?
- Will the waiver on requiring cerebrospinal fluid abnormalities open the way for more diagnostic errors in patients with progressive myelopathy?
- Why does a gadolinium-enhancing lesion retain its place within the criteria for dissemination in space when in fact it is a measure of lesion activity, not location?
- Can MRI dissemination in space criteria be further simplified when dissemination in time is also unequivocally present?

With regard to the last question, recent experience in one of our centres – where a cohort of patients with clinically isolated syndromes consisting predominantly of isolated optic neuritis has been systematically followed up – suggests that such an approach does indeed improve the sensitivity of an early diagnosis of multiple sclerosis whilst retaining high specificity (Swanton *et al* 2005; Table 7.6).

The reader is advised to review and adopt the amended criteria of the 2005 International Panel (Polman *et al* 2005b). We expect there to be further revisions in the years ahead. The competent neurologist with an interest in demyelinating disease will know the importance of keeping abreast of such developments and will always be aware that the highest levels of accuracy in diagnosis continue to rely on clinical thoroughness and expertise combined with a well informed application and interpretation of the available investigative techniques.

Table 7.5 2005 International Panel revisions to the McDonald diagnostic criteria for multiple sclerosis

MRI dissemination in space	Three out of four of the following: 1. one or more gadolinium enhancing lesions or nine or more T_2 lesions if there is no gadolinium enhancing lesion 2. one or more infratentorial lesions 3. one or more juxtacortical lesions 4. three or more periventricular lesions Note: (i) a spinal cord lesion can be considered equivalent to a brain infratentorial lesion; (ii) an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion; (iii) individual spinal cord lesions can contribute along with individual brain lesions to reach the required number of T_2 lesions
MRI dissemination in time	There are two ways to show dissemination in time using imaging: 1. the detection of gadolinium enhancement at least 3 months after onset of the initial clinical event, if not at the site corresponding to the initial event 2. detecting a *new* T_2 lesion if it appears at any time compared to a reference scan done at least 30 days after the onset of the initial clinical event
Diagnosis of multiple sclerosis in disease with progression from onset	1. One year of disease progression (retrospectively or prospectively determined) 2. Together with two of the following three: a. positive brain MRI (nine or more T_2 lesions or four or more T_2 lesions with abnormal visual evoked potentials b. positive spinal cord MRI (two or more T_2 lesions) c. positive cerebrospinal fluid (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Adapted from Polman et al *(2005b)*

Table 7.6 **Sensitivity, specificity and accuracy of the 2001 McDonald criteria and a set of modified criteria (as defined by Swanton *et al* 2005) after 3 months follow-up of patients with clinically isolated syndromes for conversion to clinically definite multiple sclerosis within 3 years**

	True positive	False positive	True negative	False negative	Sensitivity	Specificity	Accuracy
McDonald criteria for multiple sclerosis: brain MRI only	18	3	48	21	46%	94%	73%
McDonald criteria for multiple sclerosis: brain and cord MRI	18	3	48	21	46%	94%	73%
Modified criteria for multiple sclerosis: brain MRI only	29	4	47	10	74%	92%	84%
Modified criteria for multiple sclerosis: brain and cord MRI	30	4	47	9	77%	92%	86%
McDonald criteria for disseminated in space: brain MRI only	30	11	40	9	77%	78%	78%
McDonald criteria for disseminated in space: brain and cord MRI	31	11	40	8	79%	78%	79%
Modified criteria for disseminated in space: brain MRI only	35	13	38	4	90%	75%	81%
Modified criteria for disseminated in space: brain and cord MRI	37	15	36	2	95%	71%	81%
McDonald criteria for disseminated in time	19	5	46	20	49%	90%	72%
Modified criteria for disseminated in time	30	6	45	9	77%	88%	83%

True positive = criteria positive and clinically definite multiple sclerosis.
Sensitivity = true positive/true positive + false negative.
False positive = criteria positive but not multiple sclerosis.
Specificity = true negative/true negative + false positive.
True negative = criteria negative but not multiple sclerosis.
Accuracy = true positive + true negative/true positive + false positive + true negative + false negative.
False negative = criteria negative but clinically definite multiple sclerosis.

McDonald criteria for disseminated in space: three out of the following four features:
- *nine or more T_2 brain lesions or one or more gadolinium enhancing lesion*
- *one or more infratentorial lesion[a]*
- *one or more juxtacortical lesion*
- *three or more periventricular lesions*

(One spinal cord lesion can substitute for one brain lesion).

Modified criteria for disseminated in space: one or more T_2 lesions(s) in two or more of the following regions:
- *periventricular*
- *juxtacortical*
- *infratentorial[a]*
- *spinal cord.[b]*

a, excluded in cases of brainstem syndrome; b, excluded in cases of spinal cord syndrome.

McDonald criteria for disseminated in time: one or more new gadolinium enhancing lesion.
Modified criteria for disseminated in time: one or more new T_2 lesion.

Adapted with permission from Swanton et al *(2005).*

responses. Innate responses act immediately on microbial intruders, but their discrimination between the pathogenic agents and the surrounding self tissue is blunt, and their efficiency is leaky. The adaptive immune response is much more sophisticated. It has the capability to focus exclusively on the one pathogenic structure that acutely threatens the organism, while exquisitely it spares the body's own cells. The agents of the adaptive immune response are lymphocytes – T and B cells. With specific sensors on their surface, antigen receptors, lymphocytes can identify any foreign structure, and mount an appropriate response. Each lymphocyte family (clone) has one particular receptor for one particular antigen structure. Since the immune system holds millions of different lymphocyte clones, the diversity of antigen receptors is almost infinite. Each foreign structure finds a complementary receptor preformed in the immune repertoire, and binding of the antigen to this specific receptor triggers an immune response with the aim of destroying and eliminating the antigen.

But how does the immune system spare all the cells and proteins of its own organism? Why, for example, is a piece of skin accepted, when grafted from one part of the same body to another, but rejected when transplanted to another individual? The answer is because the immune system tolerates self tissues. Tolerance to self is learned, whilst diverse immune repertoires are being generated in the thymus (T cells) and the bone marrow (B cells). During maturation, most lymphocytes with self-specific receptors are eliminated in the thymus or bone marrow as soon as they encounter their specific self-antigen.

Self-tolerance by deletion is, however, not absolutely fail-safe. Quite a number of autoreactive lymphocytes, including those specific for brain autoantigens, sneak through the self-tolerizing checkpoints and settle in the healthy peripheral immune repertoire. In most people, lymphocytes with autoimmune potential are innocuous throughout life. They remain in a state of rest, first, because they do not encounter the specific autoantigen under particularly stimulating circumstances; and, second, because they are held in check by counter-regulatory suppressor T cells. However, these lymphocytes can unfold their autoimmune potential when accidentally activated, often in connection with microbial infections. Only upon such activation, does a self-reactive lymphocyte become autoaggressive. It should be noted that a large spectrum of microbes, especially viruses and bacteria, may activate autoimmune lymphocytes under particular, permissive conditions. The autoimmune receptors of lymphocytes may erroneously bind a microbial antigen, which structurally resembles the myelin autoantigen. Alternatively, microbial 'superantigens' – proteins which activate groups of T-cell receptors in an antigen-independent fashion – may preferentially stimulate autoimmune T cells. Most important, however, are mechanisms that amplify the local microenvironment. Responses of the innate immune system against microbial components (microbial oligonucleotides and membrane products, such as endotoxin or polysaccharides) may create a milieu of local inflammation that indirectly results in the activation of resting autoimmune T cells. Under these conditions, antigen-presenting cells may become increasingly efficient, and the suppressor T cells lose their counter-regulatory power. It should be noted that all these microbial mechanisms can be triggered by nonspecific infections, in the absence of a particular 'multiple sclerosis' agent.

How do activated autoimmune lymphocytes attack the central nervous system tissue? Briefly, they use the immune apparatus which is so efficient in neutralizing and eliminating exogenous agents, or newly arising tumours. Activated T cells can act on neural cells, directly or indirectly, by recruiting ancillary macrophages or microglial cells. They secrete inflammatory cytokines, such as tumour necrosis factor-α, which impede neural or glial function, or, in the case of $CD8^+$ cytotoxic killer T cells, attach to central nervous system cells and destroy them via the release of perforin. Other inflammatory mediators, cytokines and chemokines, attract macrophages and activate these to produce an additional set of inflammatory mediators, leading to the lysis and phagocytosis of the incriminated organisms.

Viewing the immune system as it reacts against foreign and even self structures may look pretty frightening. Indeed, the immune system and its connected inflammatory responses constitute a formidable fighting machinery, primarily evolved to keep the body free of microbial and other menaces. However, inflammation has its beneficial side. Inflammatory responses, be they controlled by autoimmune reactions or antigen independent, are critically required for tissue regeneration. Skin wounds, for example, are inflamed irrespective of bacterial superinfection, and the inflammation accelerates wound healing. It is known that inflammatory and immune cells produce and deposit mediators, such as neurotrophic factors, in the central nervous system that protect neuronal cells from exogenous injury and help them to function and survive. This makes it difficult to assess the actual character of an inflammatory infiltrate within the brain parenchyma. Inflammatory infiltrates in multiple sclerosis may be detrimental, by inducing tissue damage, but simultaneously may stimulate remyelination and repair.

COMPLEXITY AND HETEROGENEITY IN MULTIPLE SCLEROSIS

Everyone working in any area of multiple sclerosis research is confronted by the profound variability of the disease. Clinically the manifestations are unpredictable, as is the course and response to treatment. The pathophysiology is complex. Major differences are seen between patients in the structural features of lesions, and in the evidence for defined immunological mechanisms responsible for tissue injury. These complexities correlate with various different factors, such as the age and gender of the patients, the stage and severity of the disease, the genetic background of the patients, and (as seems likely) exposure to environmental factors.

A question that needs to be defined carefully is whether this reflects complexity or heterogeneity. By complexity, we mean the situation in which the same root cause subsequently evolves through different pathways to produce phenocopies – defined at the pathological, clinical and radiological levels. By heterogeneity, we infer a situation in which specifically different aetiological conditions (susceptibility genes and environmental triggers) determine altogether different disease mechanisms that nonetheless converge on a single set of clinical and radiological features fitting within the spectrum of one disorder.

Pathology reveals disease complexity on several different levels. As discussed above, the pathological substrate of focal white matter lesions, which mainly occur in acute and relapsing

attention, motivation, mood and goal setting in neurorehabilitation by adopting the principles of cognitive neuroscience; and using technologies that both explore and may themselves modulate brain function including, for example, transcranial magnetic and deep brain stimulation. Experimental work has already established that interventions must be 'taught to work' by behavioural techniques if the desired improvements in function are to follow the restoration of structure. These and many related matters are usefully summarized in a report with supporting evidence on restoring neurological function from the United Kingdom Academy of Medical Sciences (2004).

Disease-modifying treatments

The immediate aim of disease-modifying treatments is to inhibit disease activity, but the hope is that this will also limit the accumulation of disability and prevent the onset of disease progression. We began our discussion of these agents (Chapter 18) with an established view of the pathogenesis, having inflammation as the pivotal process from which all other aspects of tissue injury follow. We assumed that genetic predisposition and environmental triggers initiate an inflammatory process sustained through immunological mechanisms – a 'hit and run' scenario rather than persistent (viral) infection. For over a decade the emphasis of disease-modifying therapy has therefore focused more or less exclusively on immunological therapies. As we move from an entirely empirical to a more rational basis for treatment, consolidating the validity of this central inflammatory hypothesis becomes more crucial, but it has recently been challenged. Tissue remote from areas of macroscopic inflammation is abnormal; lesions sampled ultra-early in the course show loss of oligodendrocytes in the absence of inflammatory injury; and suppression of inflammation in chronic multiple sclerosis rarely does much to limit the accumulation of disability through sustained progression. Superficially, these observations question the central dogma of multiple sclerosis as a disorder in which the priority is for suppression of the inflammatory process.

But if inflammation does trigger a cascade of secondary consequences in multiple sclerosis, it follows that there is all the more reason to anticipate those events, and prevent the dominoes tumbling, by limiting the process before the onset of irreversible tissue injury. But how early is early? The establishment of a definite diagnosis – the prerequisite for any aggressive anti-inflammatory therapy – has, using traditional clinically based criteria, taken place after the disease has already caused tissue injury in the central nervous system, perhaps over several years. The development of new criteria (W.I. McDonald *et al* 2001) that use laboratory investigation – in particular neuroimaging findings – now enables earlier diagnosis in a substantial number of patients, even within 3 months of a first characteristic clinical episode. Such criteria will facilitate earlier disease-modifying treatment although, even at the first clinical manifestation, it is apparent from magnetic resonance imaging that, in many patients, the pathological process is already well established. We continue to debate whether the use of MRI criteria to confirm 'definite multiple sclerosis' after intervals as short as 12 weeks merit becoming the accepted standard.

Having reaffirmed the rationale for early anti-inflammatory treatment, it is logical to look more imaginatively at steps in the cascade of events leading to tissue injury at which a spanner might most effectively be placed in the immunological works. By analogy with success achieved in the drug management of some malignancies, there may be a place for induction of a clinical effect with a more intensive immunosuppressant followed by maintenance therapy using one or other of the licensed medications. Many drug combinations can be contemplated and, given the freedom to prescribe, their use seems inevitable, but we advocate caution in instituting polypharmacy. There is now a proliferation of 'head-to-head' trials comparing many established cocktails containing symptomatic treatments (theoretical and empirical), licensed treatments and immunosuppressive agents (usefully summarized, as at 2004, by Gonsette 2004). It is clear that many of these trials are significantly underpowered and others, we predict, will be terminated early because of apparent evidence of short-term efficacy, leaving open the question of whether there is a lasting therapeutic advantage from drug combinations with respect to disability or brain atrophy.

We have set out a sufficiently detailed account of the immunological synapse (Chapter 11), and the structure-function relationships of axons and glia (Chapters 10 and 13), for the reader to see that there is no shortage of candidate molecules or pivotal pathways at which new treatments might be targeted. The options have been rigorously catalogued, covering all the options (Hohlfeld 1997; Nepom 2002) or selected therapeutic targets (Opdenakker *et al* 2003). Suffice it to say that the zones where therapies are most likely to be deployed (and the category of medicine that will most probably be used) would include the following:

- depleting the systemic lymphocyte pool and inducing immune tolerance (monoclonal antibodies, immunosuppression, pheresis technology)
- increasing the regulation of T cells (cytokine-based therapies, immune tolerization)
- restricting the movement of activated T cells across endothelial barriers (monoclonal antibodies and small molecules, corticosteroids)
- preventing the diffusion of cells into the brain parenchyma (chemokine-based treatments)
- limiting antigen presentation and microglial activation (cytokine-based treatments, monoclonal antibodies)
- protecting intact myelinated axons from activated macrophages/microglia (macrophage inhibitors)
- inhibiting the establishment of immunological chronicity (anti-B cell and monoclonal antibodies)
- protecting intact axons from acute injury (anti-excitotoxic and membrane stabilizing agents)
- providing trophic support of persistently demyelinated axons (growth factors and remyelination strategies that might include pharmaceutical strategies for enhancing remyelination)
- promoting plasticity and axon regeneration (extracellular matrix molecules and manipulation of inhibitory environments).

PROSPECTS FOR THE TREATMENT OF PROGRESSIVE MULTIPLE SCLEROSIS

If axonal loss and inflammation are independent pathologies, then no single immunotherapy is likely to influence progression of disability; but if axons degenerate directly as a result of the

inflammatory process, or indirectly through loss of trophic support normally provided by cells of the oligodendrocyte lineage; the dividend from early suppression of inflammation may be considerable; and if the naked axon is resistant to the inflammatory milieu but has poor survival properties, strategically timed interventions leading to enhanced remyelination may also be directly neuroprotective. In Chapter 10, we challenged the dogma that rigidly separates the immunological and neurobiological components of tissue injury in multiple sclerosis. Clearly the nervous system does much to limit and contain the inflammatory process. We emphasized that molecules traditionally considered part of the immunological repertoire nevertheless act on cell-based structures in the central nervous system. Conversely, neurotrophins provide autocrine protection from inflammatory mediators, and have their own short-range immunosuppressant properties. Here, therefore, are endogenous mechanisms for limiting the potential damage to viable but threatened neurons and myelinated axons in the vicinity of an inflammatory focus, sealing the area of damage and creating the sharply demarcated lesions that characterize the pathology of multiple sclerosis. Thus, it follows that a clever course has to be steered in limiting those aspects of the inflammatory response that contribute to tissue injury, without compromising benefits for tissue repair. Furthermore, combining anti-inflammatory and neuroprotective treatments may be a sensible strategy for disease-modifying therapy throughout the clinical course. Taking the evidence gathered from a variety of clinical and experimental sources, our position is:

- The areas of focal damage, constituting plaques, are driven by inflammation; it remains to be shown that diffuse injury of normal-appearing white matter has a cause other than inflammation resulting in microglial activation.
- Regions of the central nervous system or the brain and spinal cord as a whole may have an intrinsic vulnerability to damage – a neurodegenerative diathesis – resulting from genetic or environmental events but this vulnerability nevertheless needs to be exposed by inflammation: the pathogenesis is not primarily and independently neurodegenerative.
- The impact of inflammation is conditioned by the prior state of the inflamed tissue: previously damaged regions are further injured by a minimal amount of active inflammation; intact tissue has a higher threshold and resists this potentially pathological insult.
- At the extremes of this interplay, the early stage of the disease is entirely inflammatory whereas, in the end, axon degeneration through loss of trophic support may proceed in the absence of ongoing inflammation.

The therapeutic implications of this analysis for disease progression are self-evident (Figure 19.1). There is no evidence that any form of currently available treatment alters the natural history of primary progressive multiple sclerosis. We take an equally reserved position on the success from current strategies for altering the natural history of secondary progression, once transition from the relapsing–remitting phase is unambiguously established. As a result, individuals with progressive multiple sclerosis feel disenfranchised, and their needs not well served by the recent attention to other disease types. Discouraged by the spectacle of their slow decline, these patients regularly remind neurologists that they are keen to participate in trials. Recent epidemiological evidence suggests that the clinical decline is similar in both primary and secondary cases once a moderate, fixed degree of disability has accumulated, suggesting that relapses do not significantly impact the rate of progression after this threshold has been crossed (see Chapter 4). Once a patient has entered the secondary progressive phase of multiple sclerosis, the emphasis shifts to neuroprotection – although, as set out above, we do not exclude a modest further contribution from the suppression of inflammation.

Aside from the measures we would like to see explored for acute axonal protection (see above), the mechanisms of chronic axonal attrition need separate consideration. If axons die from loss of trophic support and exquisite sensitivity to residual inflammation, it follows that replacing the missing trophic factors should be tried. But first, the trophic factors must be identified and catalogued. To date, we have IGF-I and glial cell line-derived neurotrophic factor (GDNF) on the list but others are bound to be added. Perhaps the characterization will never be complete or adequate, in which case the best dressing for threatened axons is myelin.

REMYELINATION AND AXON REGENERATION

Remyelination occupies a special role in ideas on the treatment of multiple sclerosis. To the affected person, it is an icon of hope – a holy grail – sustaining the vision of reversing chronic deficits and thereby rewriting the neurological natural history. For the clinical scientist, remyelination seems the neatest trick for protecting axons in the chronic stages, both through the direct provision of trophic support and in order to raise the threshold for further injury from residual inflammatory activity. In addition, if axonal outgrowth and connectivity could be ordered in the context of late chronic multiple sclerosis through one or other of the neurobiological strategies suggested from the identification of inhibitory molecules and growth support, it would be necessary to clothe these fragile processes with myelin in order to restore function. This analysis lifts the status of remyelination above that of a luxury – icing on the therapeutic cake – to one in which it plays an essential part in any coherent strategy for limiting and reversing the clinical deficits that invariably accumulate once recovery from the individual episode proves incomplete. The extent to which endogenous remyelination already contributes to clinical recovery, and the factors that determine the dynamics of this process, are discussed in Chapters 12 and 13. Failure of remyelination, and the reasons for this limitation from the experimental perspective, are set out in Chapter 10. So what are the prospects for making progress with this much discussed aim? It is convenient to list the issues:

- Will cessation of the inflammatory process allow sufficient repair and reversal of deficits or is assistance needed?
- Do remedies already exist that promote remyelination?
- Does suppression of the inflammatory process inhibit remyelination?
- Are some individuals good, and others bad, remyelinators; and if so, might this propensity change with time?
- Is the potential for enhancing endogenous remyelination real enough to make the concept of exogenous rescue unnecessary?