RACHELLE FISHMAN–MATTHEW MOORE LECTURE

The Pathological and Clinical Dynamics of Multiple Sclerosis

W. I. MCDONALD, M.B., PH.D., FRCP

Abstract. The application of magnetic resonance imaging, spectroscopy and electrophysiological techniques to the study of multiple sclerosis has enhanced our understanding of the mechanism of relapse and remission. The earliest detectable event in the development of a new lesion is an increase in permeability of the blood-brain barrier associated with inflammation. Demyelination occurs early in the inflammatory phase. Both processes contribute to conduction block and functional loss. When the inflammation subsides, edema resolves and conduction is restored probably as a result of the expansion of sodium channels into the demyelinated axon. Remyelination is not essential to remission. Wallerian degeneration may be an important factor contributing to irreversible deficit.

Key Words: Degeneration; Demyelination; Evoked potentials; Inflammation; MRI; MRS; Multiple sclerosis.

INTRODUCTION

One of the outstanding features of multiple sclerosis (MS) is its variability. It varies in the same patient at different times: early in the course of the disease periods of disability alternate with longer or shorter periods of virtually complete normality. Later there is usually an accumulation of deficit, partly from incomplete recovery from individual relapses, and partly from an insidious progression—the secondary progressive form of the disease. There is also striking variability between patients: in some the disease runs a benign course for many years (I have patients without serious disability after 50 years), while in others death comes within a year of onset. There is, moreover, the mysterious and infrequent primary progressive form of the disease which progresses steadily and ineluctably from its inception.

Variability then is the outstanding clinical feature of MS, which raises the fundamental question: What are the pathological and physiological mechanisms which determine its course? It is this issue which I shall address here.

The major difficulty in relating the rich pathological variety found at postmortem to the varying clinical states has been the inaccessibility hitherto of the brain and spinal cord to pathological study during life. The position has recently changed radically because of technical advances which allow non-invasive monitoring of pathological and physiological events. I have been fortunate to be involved with the exploitation of both. What is easy and obvious now was not always so and I shall therefore consider our present understanding in its historical context. I propose to explicate three features of the disease: relapse, remission, and the development of irreversible deficit.

PATHOGENESIS OF THE MS LESION

The first depiction of the lesions of MS was by Cawell (1), and the first association of a case history with a pathological description came soon after from Cruveilhier (2, 3). It was Valentin (4), however, who first recognized the relapsing and remitting character of the disease. Demyelination was first illustrated by Frohmann (5) a decade later, of whose work Charcot (6) dryly remarked, "In reference to the examination of a small fragment of spinal cord [Frohmann has] written a large volume," though he did add appreciatively that it was "adorned with remarkable plates and enriched with valuable documents."

It was, of course, Charcot himself who, the next year in 1868, pulled together the observations that he and his predecessors in England, Germany and France had made (7). He emphasized four principal elements in the lesion: demyelination, relative preservation of axons, gliosis and a variable amount of inflammation. The questions for us as for the 19th century investigators is "How does the nervous system get into this state, and how do these changes produce the clinical picture?" In the mid 19th century there were two conflicting hypotheses about the pathogenesis of the MS lesion: those of Rindfleisch and Charcot. Rindfleisch (8) held that the primary cause of the disease lay "in an alteration of individual vessels and their ramifications . . . [which] . . . are in a state characteristic of chronic inflammation."

Charcot, however, took a different view, stating: "It is evident, however that this explanation only sets the difficulty a little further back. . . . Undoubtedly the multiplication of nuclei and the concomitant hyperplasia of the reticulated fibres of the neuroglia constitute the initial, fundamental fact and necessary antecedent; the degener-
erative atrophy of the nerve elements is consecutive and secondary. . . ."

Thus we have two contrasting views: that inflammation is primary and leads to demyelination or, alternatively, that inflammation is secondary and results from myelin breakdown produced in some other way. The discovery that autoimmune demyelination produced experimentally depends on an inflammatory mechanism has, by analogy, lent weight over the past two decades to the inflammatory hypothesis (10). Direct evidence in man has been lacking because of the inaccessibility hitherto of the central nervous system during life. Now the use of serial magnetic resonance imaging (MRI) has tipped the balance very much in favor of Kindlirsch's view.

Magnetic Resonance Imaging

It is now well established that some 98% of patients with clinically definite MS show abnormalities on MRI which correspond with plaques at postmortem (11–13). It soon became clear, however, that there was more to the story than this. First, there could be a striking waxing and waning in the size of lesions over a matter of weeks (14, 15). Second, the use of the enhancing agent gadolinium-DTPA (Gd-DTPA) showed that at any given time, some lesions enhance and some do not (16).

The significance of the variability in enhancement was explored in studies of chronic relapsing experimental allergic encephalitis (EAE) in the guinea pig (17). Enhancement was readily demonstrated in spinal cord lesions, and its presence was found to be associated invariably with the presence of inflammation. The distribution of inflammation at postmortem in MS—sometimes at the center of small lesions, sometimes circumferentially around larger, completely demyelinated areas—raised the possibility that in the human disease, as in the experimental disease, enhancement was indicating the presence of inflammation. This conjecture was confirmed in a patient who died some 10 days after a Gd-DTPA-enhanced MRI (18).

Against this background, it is appropriate to consider the natural history of the individual lesion. This we have been able to do in the course of carrying out frequent serial Gd-DTPA-enhanced MRI in patients with different clinical forms of MS. On more than 30 occasions we have seen the following sequence of events. The earliest detectable change is an increase in permeability of the blood–brain barrier which, for the reasons just given, we interpret as being associated with inflammation. An area of abnormality visible without enhancement appears within the next week or two (19, 20) which increases in size to a maximum at 4–6 weeks. Enhancement ceases after approximately a month and the area of abnormal signal diminishes over several weeks to leave a smaller residual lesion.

The dynamics of the process are highlighted by comparing enhanced and unenhanced scans over a 6 month period. New disease activity (either the appearance of new lesions or re-enhancement in pre-existing lesions) is five to ten times more common than clinical relapse (14, 15, 21, 22). At any one time, several lesions may be seen in different stages of evolution, and sometimes clusters of lesions may appear together at a single level in the brain (21). In other areas, at the same time, there may be no disease activity. In one of our patients, a 26-year-old woman in the secondary progressive phase of the disease, there were 97 separate areas of enhancement over a 9 month period, but only three clinically expressed relapses. These observations raise a number of questions. I shall deal with three.

What Are the Dynamics of Demyelination?

I have stressed the waxing and waning of enhance-
ment, i.e. of the inflammatory process. When does demyelination occur? Two lines of evidence suggest that it occurs early in the inflammatory phase.

Proton MRS: Myelin is not visible with standard MRI because the proteolipid protons are tightly bound. Theory predicts that the protons in myelin breakdown products should be detectable by proton spectroscopy. It is now possible to record reliable spectra from volumes as small as 1.3 cm³ (a not uncommon size for MS lesions) and thus to determine the relative concentrations of a number of compounds. The initial studies of MR spectroscopy (MRS) in MS relied principally on long echo resonances which do not show peaks in the region of 0.9 and 1.3 parts/million where lipid peaks would be expected. Low peaks are, however, visible here using short echo spectroscopy (23). The interpretation that lipid makes an important contribution to these peaks (as suggested by the position of peaks produced by pure lipid in vitro) was supported by finding very large peaks in the same position in the spectrum from a lipoma of the quadrigeminal plate (23).

Davie et al (23) carried out serial observations in eight patients. Four were undergoing Gd-DTPA-enhanced MRI at monthly intervals in the course of another study. In these four it was possible to carry out MRS on new enhancing lesions which must have been less than a month old. In all, and in four other enhancing lesions, the age of which was not known, there was a striking increase in the area of the lipid peaks. This increase persisted after enhancement ceased, but diminished to control levels after a mean of 5 (range 4–8) months, a time course corresponding with that of the disappearance of myelin breakdown products in other conditions (24).

Evoked Potentials: The second line of evidence comes from a combination of evoked potential and Gd-DTPA-enhanced MRI (25). As I shall show shortly, the presence of a marked delay in the visual evoked potential within 2 days of the onset of symptoms and at a time when the
nerve is enhancing indicates that demyelination occurs very early in the inflammatory phase. But the question remains, is it primary or secondary? The occurrence of perivenous sheathing in the periphery of the retina (where there is no myelin) in about a quarter of patients with isolated optic neuritis (26) or MS (26, 27) shows that the presence of nearby myelin breakdown products is not a prerequisite for the development of inflammation. This observation is consistent with the notion that inflammation is primary, but crucial evidence that it is so is lacking. What can be stated with reasonable confidence, however, is that inflammation is currently the earliest detectable event in the development of a new lesion and that demyelination occurs early in its evolution.

What Is the Nature of the Disappearing Element and of the Residual Lesion?

Using the technique of T2-magnetization decay analysis it is possible to distinguish edema, gliosis and cell loss in vivo. Barnes et al (28) showed that the acute va- sophic edema produced by the application of a cold probe to the exposed dura in the cat is characterized by a biexponential T2-magnetization decay curve, indicating that the water protons are in two compartments which are not freely communicating, viz. the intracellular and extracellular spaces. The "disappearing" element of the acute MS lesion has the same characteristics, from which one may infer that, as expected, this component of the lesion is due to edema (29 and D. Barnes, unpublished observations).

After some weeks, gliosis develops and the extracellular space returns to the same small size as in normal white matter. The T2-magnetization decay curve is now monoeponential (as in normal white matter), the extracellular protons being too few in the small extracellular space to detect by this method.

Barnes et al (30) next investigated lesions which were known to be more than 2 years old because they had been studied previously. Approximately half had monoeponential T2 decay and half biexponential. In both types, the T2 was increased. In experimental lesions there is a characteristic change in the ratio T1/T2 produced by gliosis, and this change was seen in the monoeponential lesions. It was therefore predicted that the monoeponential lesions were predominantly gliotic, and the biexponential lesions would have a markedly increased extracellular space. This was something of a surprise, but the reality of the prediction was confirmed in sections from postmortem material kindly made available by Dr. John Prineas. Both types of lesion were found (30). The expansion of the extracellular space was moreover found to be due to axonal loss. From these observations we may conclude that the acute lesion of MS resolves into a highly cellular, gliotic lesion and that many later lesions show extensive axonal loss.

We have followed the lesions structurally from the earliest detectable change—inflammation—through to the chronic residual scar with its varying proportions of gliosis, persistent demyelination and axonal loss, and we come now to the third question.

What Are the Effects of This Sequence of Pathological Changes on Function?

Charcot (7) had predicted in 1868 that demyelination would interfere with conduction, but the first demonstration that this was so was that of Denny-Brown and Brenner (1944) in relation to peripheral nerve injury. They concluded that the failure of a muscle to contract after stimulation above the site of compression was due to conduction block produced by the demyelination they found histologically. I was able to confirm this directly in the early 1960s in experiments with diphtheritic neuropathy suggested by Professor A. K. McIntyre, and by studying single fibers, to show that when conduction survived it was slow (31). Sears and I later showed that the same effects are seen after demyelination of central nerve fibers (32).

The next step was to apply these results to man. It had been known since the mid 1930s that human peripheral nerve has a compound action potential resembling that of an animal nerve, and in the 1960s it was shown that nerve conduction studies can give a guide to pathology. I therefore suggested in 1971 to Martin Halliday that we might see whether the visual evoked potential could be used in a similar way in optic neuritis. It was clear from the first three cases that it could (33). Much subsequent work has confirmed those early observations. In the acute stage there is a reduction in amplitude and an increase in latency. Caution is necessary when extrapolating from single fiber studies to evoked potentials which are mass responses mediated by large numbers of synapses, but there is good evidence that a reduction in amplitude principally reflects conduction block and that slowing due to demyelination makes an important contribution to the increase in latency.

Optic neuritis is a useful model in which to explore the contribution of the acute elements of the pathological process to conduction changes and symptom production in demyelinating disease. Using appropriate imaging techniques, it is easy to detect the lesion of optic neuritis and Gd-DTPA enhancement in the optic nerve. Youl et al (25) studied ten patients within 2 weeks of the first onset of the symptoms in optic neuritis. All 11 affected nerves (one case had bilateral involvement) enhanced; a month later all but two had ceased to do so. The clinical features of the optic neuropathy were associated with the enhancing (inflammatory) phase. Of particular interest were the evoked potential results. When a response was recordable in the acute stage there was a marked reduction in amplitude and an increase in latency, indicating
both conduction block and demyelination. After enhancement ceased, the delay persisted but the amplitude returned toward normal. The fact that demyelination was present at both times but evidence of inflammation was present only in the acute stage suggests that whatever contribution demyelination was making to the conduction defect, the inflammatory process itself was playing a crucial role. The mechanism is uncertain but may be mediated by cytokines (34), some of which are known to affect channels in excitable membranes (35, 36).

An important implication of these findings is that persistently demyelinated fibers must be able to conduct, and the question arises as to the mechanism. In the peripheral nervous system, continuous or microsallatory conduction can develop in demyelinated axons (37, 38). There is evidence that this is due to an increase in the number of sodium channels in the internodal axons (39) and England et al. (40) have demonstrated a spread of Saxotoxin binding from the nodes into the internodal region in demyelinated single fibers. Very recently it has been convincingly demonstrated that persistently demyelinated central fibers too can acquire the capacity to conduct (W. Levick & W. Carroll, unpublished observations). It is probable that similar changes occur in MS: virtually complete demyelination of the optic nerves is compatible with reading—admittedly with telescopes (41)—and an increase in tritiated Saxotoxin binding (indicating an increase in sodium channels) has been demonstrated at postmortem in plaques remaining rich in axons, but not in those with severe axonal loss (42).

I said at the outset that I wished to explore the mechanism of three of the cardinal clinical features of MS. Let us see how far we have got. First, relapse. The earliest detectable change is inflammation accompanied by demyelination. Both processes contribute to conduction block and functional loss. Thus, we have established the main pathological and physiological events in the development of the relapse. After a month, inflammation subsides, edema resolves and conduction is restored. The persistent delay in the visual evoked potentials in the great majority of patients indicates that demyelination persists, and it seems likely that the principal mechanism of remission is the development of conduction in persistently demyelinated fibers, probably as a result of the extension of sodium channels into the demyelinated axon.

Prineas et al. (43) have recently demonstrated convincingly that remyelination, so scanty at postmortem in longstanding cases, is more extensive in patients dying within 6 months of the onset of MS. This observation fits nicely with our observation in children that after optic neuritis more than 50% have a normal latency of the visual evoked potential (44). Such remyelination would be expected to help toward full recovery, but given that delays persist in the face of good clinical recovery in 90% of adults, I think it unlikely that it plays a major part in the mechanism of early remission. I come now to my last question.

What Is the Mechanism of Irrecoverable Deficit?

Here we are on much less certain ground. It is not known whether conduction in persistently demyelinated fibers continues indefinitely, or whether a second or further episode of inflammatory demyelination—which our serial studies show is common and convincing, postmortem evidence for which has recently been provided by Prineas et al. (45)—might irreparably impair the capacity of the axons to recover or indeed might actually breach their continuity leading to Wallerian degeneration.

That axonal degeneration occurs in many chronic lesions is certain. There is also a persistent low grade increase in permeability of the blood–brain barrier, often not visible as enhancement but detectable as T2 shortening after Gd-DTPA injection (30). The question whether this represents chronic low grade inflammation or lasting damage to the endothelium without continuing inflammation remains to be resolved.

What we do know, however, is that the capacity for recovery once axons are lost is much more limited than when they survive. Our hypothesis is that it is the development of axonal degeneration that leads to the emergence of irrecoverable deficit. Three lines of evidence suggest that this may be correct. First, there is the common observation of severe loss of the retinal nerve fiber layer in association with poor vision after multiple attacks of optic neuritis. Second, Kidd et al. (46) have shown that there is a good correlation between quantitative measures of motor disability and reduction in cross-sectional area of the cervical spinal cord, a well-known consequence of Wallerian degeneration. Third, Filippi et al. (47) have recently compared the T2-magnetization decay characteristics of large lesions in cases of benign MS with those in the secondary progressive form. A significantly higher frequency of biexponential curves—indicating an expansion of the extracellular space which from the pathological evidence presented above can be attributed to axonal loss—is found in the more disabled patients.

None of these observations is decisive, and we are currently involved in a major effort to clarify the mechanism of the later clinical decline seen in so many patients with MS.

PRIMARY PROGRESSIVE MS

The account of the pathological and clinical dynamics of MS I have given is based on the common forms of the disease characterized by relapse and remission with or without an evolution to secondary progression. The question arises whether the primary progressive form of the disease is pathogenetically the same. An answer to this question has become pressing since the recent demonstration of the relative effectiveness of beta-interferon.
in treating relapsing/remitting disease (48, 49). There are important differences in the clinical and MRI characteristics (21). A comparison of twelve patients with the primary progressive form of the disease with twelve carefully matched patients with the secondary progressive form of the disease showed that in the former, new lesions were significantly less frequent over a 6 month period and that gadolinium enhancement occurred in only 5% of new lesions, compared with 87% in relapsing and remitting disease. These observations do not necessarily mean that the lesion in primary progressive MS is not inflammatory in nature. If the enhancement had been of very short duration, it might have been missed because the shortest scanning interval was 2 weeks. Alternatively, if the areas of enhancement were much smaller, they could have been beyond the resolution of the scanner.

Because of this uncertainty Kidd et al (50) undertook a pathological comparison of four cases of primary progressive disease and five of secondary progressive disease. A total of 436 lesions was studied and the cellularity within the lesion, at the edge of the lesion and around the venules was quantified. There were indeed inflammatory cells in the primary progressive cases, but they were significantly fewer in number. It thus seems likely that at least some of the pathogenetic mechanisms in primary progressive MS are similar to those in the relapsing/remitting and secondary progressive forms of the disease. Why clear-cut cycles of disease activity and inactivity are absent in primary progressive MS remains an important unanswered question.

CONCLUSION

One of the outstanding contributions of the American Association of Neuropathologists, which Dr. Matthew T. Moore has so notably supported, is its emphasis at its meetings and in the Journal of studies of disease mechanism. In this lecture I have tried to show how important insights into pathogenesis have been gained by combining clinical and laboratory approaches. The exploitation of the potential of magnetic resonance methods for revealing pathology and electrophysiological methods for assessing nerve conduction has led to the elucidation of many of the details of the clinical and pathological evolution of MS, a prerequisite for the development of rational treatment.

ACKNOWLEDGMENTS

The work of the Multiple Sclerosis NMR Research Group is supported by The Multiple Sclerosis Society of Great Britain and Northern Ireland and by the Medical Research Council.

REFERENCES

4. Valentin W. Ueber die Sclero se des Gehirns und Rückenmarks. Deutsche Klinlk 1856;8:147-51
DYNAMICS OF MULTIPLE SCLEROSIS

343


41. Wisniewski HM, Oppenheimer D, McDonald WI. Relation between myelination and function in MS and EAE. (Abstract) J Neuropathol Exp Neurol 1976;35:327


49. Pety DW, Li DKB, The UBC MS/MRI Study Group, the IFNβ Multiple Sclerosis Study Group. Interferon β-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicentre, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662–7