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SERIES PREFACE

The *Blue Books of Neurology* have a long and distinguished lineage. Life began as the *Modem Trends in Neurology* series and continued with the monographs forming *BIMR Neurology.* The present series was first edited by David Marsden and Arthur Asbury, and saw the publication of 25 volumes over a period of 18 years.

The guiding principle of each volume, the topic of which is selected by the Series Editors, was that each should cover an area where there had been significant advances in research and that such progress had been translated to new or improved patient management.

This has been the guiding spirit behind each volume, and we expect it to continue. In effect, we emphasize basic, translational, and clinical research but principally to the extent that it changes our collective attitudes and practices in caring for those who are neurologically afflicted.

Tony Schapira took over as joint editor in 1999 following David's death, and together with Art oversaw the publication and preparation of a further 8 volumes. In 2005, Art Asbury ended his exceptional co-editorship after 25 years of distinguished contribution and Martin Samuels was asked to continue the co-editorship with Tony.

The current volumes represent the beginning of the next stage in the development of the Blue Books. The editors intend to build upon the excellent reputation established by the Series with a new and attractive visual style incorporating the same level of high-quality review. The ethos of the Series remains the same: up-to-date reviews of topic areas in which there have been important and exciting advances of relevance to the diagnosis and treatment of patients with neurological diseases. The intended audience remains those neurologists in training and those practicing clinicians in search of a contemporary, valuable, and interesting source of information.

ANTHONY H.V. SCHAPIRA
MARTIN A. SAMUELS
Series Editors

PREFACE

Multiple Sclerosis 3, volume 34 of the Blue Books of Neurology series, is dedicated to the memory of the late Ian W. McDonald, who edited *Multiple Sclerosis 1* with Donald H. Silberberg and *Multiple Sclerosis 2* with John H. Noseworthy. Prof. McDonald pioneered several key areas of multiple sclerosis (MS) research, including characterization of the physiology and morphology of demyelination and remyelination of the central nervous system (CNS). He developed new laboratory methods, such as evoked potentials, to supplement the clinical diagnosis of MS, and he was among the first to envision the enormous potential of magnetic resonance imaging for dissecting the complex problems of inflammatory brain disease. He applied brain imaging and spectroscopy to improve understanding of the pathogenesis of this disorder and to evaluate new therapies. Moreover, Ian McDonald took a leading position in formulating the consensus diagnostic criteria that have since come to bear his name.

Although the clinicopathologic hallmarks of MS are well recognized, the last decade has witnessed significant clinical and scientific advances that have led to improved diagnosis and treatment as well as new insights into the pathogenesis of this enigmatic disorder. We are confident that Prof. McDonald would be delighted to see how rapidly the field has continued to grow, and we are honored to have been invited to edit this volume. We have endeavored to provide a comprehensive, clinically relevant, up-to-date summary on MS and the heterogenous spectrum of CNS inflammatory demyelinating disorders, including clinically isolated syndromes, pediatric MS, transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica. Topics discussed include natural history, diagnosis, genetics, epidemiology, neuroimaging, pathogenesis, immunology, biomarkers, gender issues, and cognitive and mood disorders. A strong emphasis on treatment is also included, with a focus on current disease-modifying drugs, attack therapy, symptomatic therapy, complementary alternative approaches, management of aggressive MS, and future immunologic and neuroprotective or reparative strategies.

We would like to express our sincere gratitude to our distinguished coauthors who have given generously of their time and expertise. We also appreciate the support from the Elsevier editorial staff (Hemamalini Rajendrababu and Adrianne Brigido) throughout the development of this text.

CLAUDIA F. LUCCHINETTI, MD
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1 Clinical Features and Natural History of Multiple Sclerosis: The Nature of the Beast

SEAN JOSEPH PITTOCK

For the practicing neurologist, knowledge of the natural history of multiple sclerosis (MS) that encompasses the overall course and prognosis is a prerequisite to the counseling of a patient who is given such a diagnosis. When confronted with the reality of MS for the first time, patients' first questions relate to long-term prognosis: What will happen to me? From a health research point of view, knowledge of the natural history of MS affects how we think about the pathophysiology of MS, guides therapeutic trial design, assists in health care economics and service provision, and provides a benchmark against which therapeutic trial efficacy can be compared.

Natural history data is best obtained from populations of patients that are representative of MS as a whole, such as all MS patients living within a well-defined geographic area. These population-based cohorts are more representative of the disease than hospital- or clinic-based cohorts, which tend to overrepresent more severe disability and may provide an overpessimistic view.

The natural history of MS is among the best studied chronic medical illnesses. Despite a wealth of information gained from large, population-based studies on clinical features predictive of future course and outcome, the ability to apply this knowledge to an individual patient to allow prediction or prognostication has been problematic.

This review focuses on recently published natural history studies, early clinical predictors of disability outcome and their application to an individual patient,

the controversy surrounding the entity of benign MS, and some recent new approaches to data set analysis with emphasis on age at disability milestones rather than time to reach disability milestones.

Disability Progression: What Happens to Patients over Time?

The evolution of MS over time is well studied worldwide, and results are generally consistent among investigators, although some recent natural history studies from North America have suggested a better global prognosis.[1,2] It is important to note that these studies have relied heavily on measures of impairment, specifically the Expanded Disability Status Scale (EDSS) score, as an outcome measure.[3] The EDSS scores range from 0 (no disability) to 10 (death). Cutoff scores most commonly used in natural history studies include mild to moderate disability, with an EDSS score of 3 (e.g., mild paralysis) or EDSS 4 (limited walking ability but able to walk without aid or rest for > 500 m); EDSS 6, which indicates the need for a cane or unilateral support and ability to walk no more than 100 m without rest; and EDSS 8 (need for wheelchair) or EDSS 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support).

TIME FROM ONSET TO DISABILITY MILESTONES

Natural history studies have focused on the time from onset or diagnosis of the disease to the assignment of one of these EDSS scores; these data provide information regarding the rate of disability progression. If one considers population-based studies of MS in general, median time from onset of MS to EDSS 3 or EDSS 4 ranged from 6 to 23 years.[1,2,4-8] Median time from onset of disease to EDSS 6 was somewhat more consistent (because need for a cane is a more robust and reliable outcome measure) and varied between 16 and 28 years.[1,5-8] Time from onset to the need for a wheelchair ranged from 30 to 52 years for population-based cohorts.[1,5,8]

In a retrospective review of prospectively collected data from all 2837 patients, followed prospectively for 22,723 patient years, registered with one of the four MS clinics in British Columbia, 21% required a cane after 15 years of disease.[2] This frequency increased to 69% by 40 years after onset. At 30 and 40 years after onset, 14% and 22% of patients, respectively, required a wheelchair.

TIME FROM ONSET TO DISABILITY MILESTONES STRATIFIED BY MULTIPLE SCLEROSIS CLINICAL SUBGROUPS

The initial course has a significant impact on the time from onset to specific levels of disability. In 1996, a formal classification of MS disease subtypes was published that has become widely accepted.[9]

- Relapsing-remitting (RR): Clearly defined disease relapses with full recovery or with sequelae and residual deficit on recovery; periods between disease relapses characterized by a lack of disease progression
- Secondary progressive (SP): Initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus

- Primary progressive (PP): Disease progression from onset with occasional plateaus and temporary minor improvements allowed
- Progressive relapsing (PR): Progressive disease from onset with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression. A more recent proposed classification is illustrated in Figure 1-1.[10]
- Another classification type used by some investigators is that of single-attack progressive (SAP) MS, in which there is a single "onset attack" followed later by a progressive course.[11]

In population-based studies, an RR onset is most frequent (95% in Olmsted County, Minnesota; 66% in London, Ontario; 87.6% in British Columbia; 85% in Lyon, France).[1,2,5,8] The frequency of conversion from RRMS to SPMS reported for the Ontario cohort increased with duration of disease (12% at 5 years, 41% at 10 years, 58% at 15 years, and 89% at >26 years).[8] Other studies have reported a lower frequency of conversion.[1,2] Frequencies of PPMS and PRMS (both of which are considered progressive from onset) vary from 9% to 19% and from 6% to 15%, respectively.[5,8]

Patients with an RR course take a longer time from onset to reach disability milestones than do patients with an initially progressive course (Fig. 1-2). Myhr and colleagues reported a 72% probability of not needing a cane after 15 years of disease for patients with RRMS, compared with only 10% for those with PPMS.[12] Similarly, RRMS patients had an 84% probability of not needing a wheelchair after 15 years, compared with 42% for those with PPMS. In the Olmsted County 2000 study, median time from onset to the need for a cane (see Fig. 1-2B) in patients who continued to have an RR course was 51 years, compared with 17.9 years for those with SPMS and 6.3 years for those with PPMS.[1] In the French population-based Lyon cohort, the median time from onset to need for a cane was

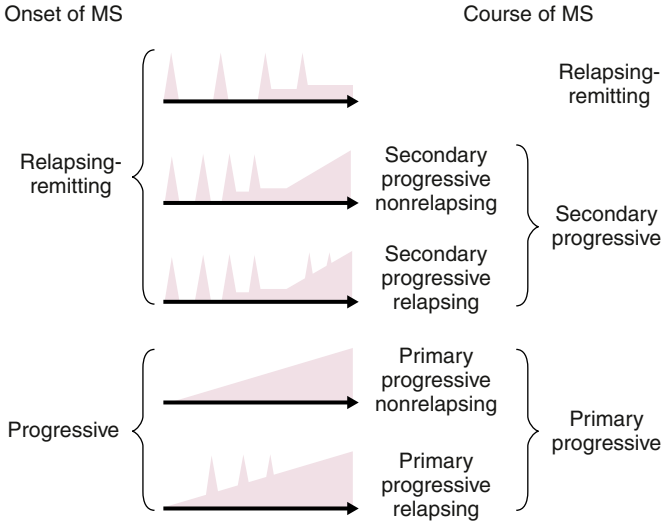

Figure 1–1 Proposed classification of the onset and course of multiple sclerosis (MS). (Reproduced from Confavreux C, Vukusic S: Natural history of multiple sclerosis: Implications for counselling and therapy. Curr Opin Neurol 2002;15:257-266, with permission of Lippincott Williams and Wilkins, online at http://www.lww.com.)

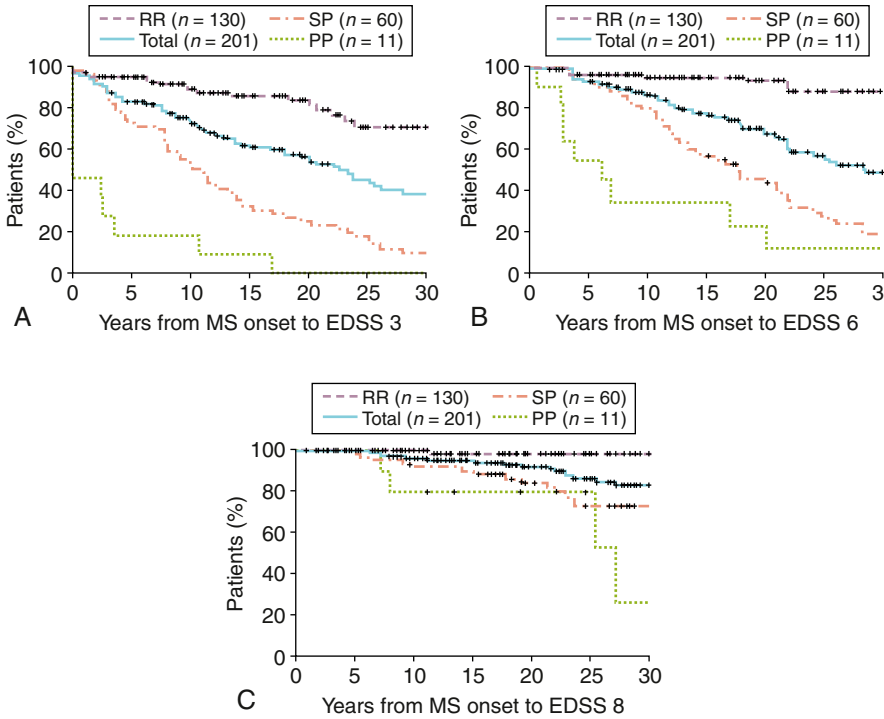

Figure 1–2 Time to Expanded Disability Status Scale (EDSS) score by multiple sclerosis (MS) subtype for the 2000 Olmsted County MS population. **A,** Years from MS onset to EDSS 3 (minimal disability but fully ambulatory). **B,** Years from MS onset to EDSS 6 (use of a cane). **C,** Years from MS onset to EDSS 8 (use of a wheelchair). RR refers to patients who continue to have a relapsing-remitting course and therefore excludes secondary progressive cases. PP, primary progressive; SP, secondary progressive. (Data from Pittock SJ, Mayr WT, McClelland RL, et al: Disability profile of MS did not change over 10 years in a population-based prevalence cohort. Neurology 2004;62:601-606.)

23 years for patients with an RR course, compared with 7 years for patients with a PP course.[5] In a recent natural history study of PPMS from British Columbia, Canada, progression of disability was slower than previously reported. The median time from onset to requiring a cane was 13.3 years; however, there was considerable variation. Although 25% of the patients had reached EDSS 6 after 7.3 years, another 25% did not require a cane after 25 years.[13]

What Affects Long-Term Disability Outcome?

A multitude of demographic and clinical variables including female gender, a younger age at onset, sensory symptoms or optic neuritis, and a monosymptomatic presentation at onset have been associated with a favorable course.[14-16] In contrast, prognostic variables associated with a poor outcome have included male gender; onset with motor, sphincter, or cerebellar features; poor recovery from initial or early attacks; higher attack rate in the first 5 years; and a

progressive course.[8,14-16] These statistically significant associations have generally been reported in the context of univariate and, less frequently, multivariate analysis. Few predictors of outcome have been reported for PPMS.[13] Although individual factors are often statistically significant when considering large population-based cohorts, their clinical prognostic applicability to an individual MS patient is much less reliable. There is little doubt that the initial course from onset is the strongest clinical predictor of how quickly a patient will reach disability milestones.

CLINICAL RELAPSES

Disease-modifying agents (DMAs) have been shown in large, randomized controlled trials to reduce the relapse rate and to reduce the accrual of lesions identified on magnetic resonance imaging.[14,17-19] Whether they have a significant clinical benefit over the long term remains unclear. For RRMS, a central and highly controversial question is whether the frequency (and severity) of relapses influences disability progression in MS.[20,21] Reported relapse rates have differed among MS studies, with prospective assessments at close intervals yielding the highest and probably the most sensitive results.[20] A yearly relapse rate of 0.5 is probably a reasonable estimate in a population-based sample of patients with RRMS.[20]

In the Ontario study, 58% of 681 patients with RR disease had one attack during the first 2 years, 21% had two attacks, and only 20% had three or more attacks in the first 2 years of disease.[22] Natural history studies from Lyon, Ontario, and Turkey have shown a weak association between number of relapses in the first 2 to 5 years and long-term disability outcome, although causality has not been established.[5,6,16] Other studies failed to conclude that number of relapses in the first few years influences final outcome, and more recent, large natural history studies have provided convincing evidence of a dissociation between relapses and disability progression.[11,21,23,24] In fact, at the Jekyll Island conference on MS clinical trial outcome measures, relapse frequency was ranked 11th in terms of perceived importance in measuring therapeutic response in MS.[25]

The Lyon group reported that, once a detectable threshold of irreversible disability (EDSS 4) was reached, the disease entered a state of uniform progression that did not appear to be influenced by the presence or absence of superimposed relapses (Fig. 1-3).[21] Patients with a progressive course from onset reached irreversible disability much quicker than patients with an RR-onset course (median, 0.0 versus 11.4 years). However, once this point of irreversible disability was reached, the times to EDSS 6 (median, 5.7 versus 5.4 years) or EDSS 7 (median, 12.1 versus 12.0 years) were similar ($P > .70$) regardless of onset course.[21] In the Olmsted County population-based study, the time to development of a clinical threshold of disability (EDSS 3), whether 2, 5, or 10 years, did not affect the rate of further progression (Fig. 1-4).[1] Among patients with PPMS, the time course of progressive disability was not significantly influenced by the presence or absence of superimposed relapses (Fig. 1-5).[21] For patients with SPMS (initially RR), the median time from EDSS 4 to EDSS 6 was similar for 292 patients without and 191 patients with superimposed relapses (4.0 versus 4.4, respectively; $P = .68$; see Fig. 1-5).[21] Surprisingly, patients with superimposed relapses had a more favorable outcome than those without superimposed relapses, with a longer time from EDSS 4 to EDSS 7 (10 versus 7.8 years; $P = .04$). Similarly, superimposed relapses were

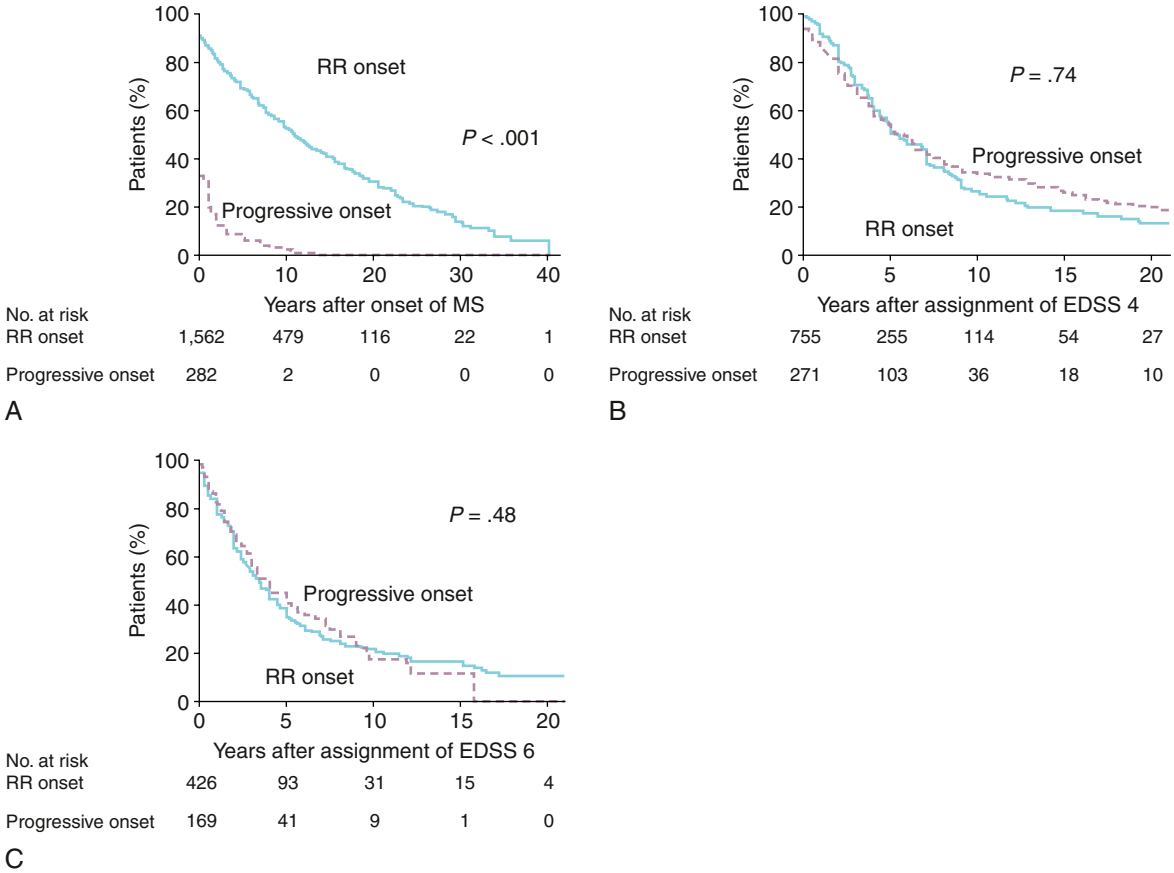

Figure 1–3 Irreversible disability, based on Expanded Disability Status Scale (EDSS) score, occurs sooner in patients with a progressive course from onset, compared with those with a relapsing-remitting (RR) course from onset, although, once irreversible disability has occurred, the time course of progressive disability is similar regardless of the initial course (relapsing or progressive). Kaplan–Meier estimates are shown for time from onset of multiple sclerosis to assignment of EDSS 4 **(A),** time from EDSS 4 to EDSS 6 **(B),** and time from EDSS 6 to EDSS 7 **(C)** among 1844 MS patients stratified by initial course. (Data from Confavreux C, Vukusic S, Moreau T, Adeleine P: Relapse, remission, and progression in multiple sclerosis. N Engl J Med 2000;343:1430-1438.)