REVIEW ARTICLE

The Natural History of Multiple Sclerosis

B.G. Weinshenker and G.C. Ebers

ABSTRACT: Studies which have attempted to define the outcome of multiple sclerosis (MS) have methodologic difficulties arising from patient referral biases and the length of follow-up required, which make prospective studies of an inception cohort unrealistic. Means to improve the validity of retrospective natural history studies are suggested. Results of existing series are summarized and compared. Survival is only rarely shortened by MS, but disability to the point of requiring aids for ambulation occurs in 30-70% of patients by 15 years from onset of symptoms. Disagreement as to the percentage of patients who are ultimately bedridden by MS likely arises in large part due to differences in patient ascertainment and follow-up. The need to develop early clinical markers for the patient at high risk for rapid development of major disability is stressed.

RÉSUMÉ: L'histoire naturelle de la sclérose en plaques. Les études qui ont tenté de définir le pronostic de la sclérose en plaques (SEP) ont des défauts méthodologiques provenant de biais de sélection des cas référés aux établissements spécialisés et de la longueur du suivi requis pour de telles études, ce qui rend les études prospectives d'une cohorte de patients en phase de début de la maladie tout-à-fait irréalisables. Nous suggérons des moyens d'améliorer la validité des études rétrospectives de l'histoire naturelle de la maladie. Nous résumons et comparons les résultats des séries existantes. La survie n'est que rarement écourtée par la SEP, mais, chez 30 à 70 % des patients, l'invalidité progresse au point où le patient a besoin d'aide à la marche en dedans de 15 ans du début de la symptomatologie. Le désaccord sur le pourcentage des patients qui sont éventuellement confinés au lit à cause de la SEP provient probablement en grande partie des différences dans le recrutement et le suivi des patients. Nous insistons sur la nécessité de développer des marqueurs cliniques précoces pour le patient à haut risque de développer rapidement un degré important d'invalidité.

Can. J. Neurol. Sci. 1987; 14:255-261

Proper conduct and design of clinical trials to study the efficacy of agents which might benefit the patient with multiple sclerosis (MS) must take into account available data on the natural history of this disease. With increasing numbers of trials designed to test such agents,[1] the ability of a given center to accumulate data on the untreated course of MS is rapidly diminishing while the need for such data is increasing. The tendency for spontaneous decrease in the relapse rate with time and the variability in outcome among individuals necessitate careful design of clinical trials with appropriately chosen endpoints and controls. Numerous investigators have studied the natural history of MS, but results are not entirely satisfactory and often conflicting. This topic has been briefly reviewed by Kurtzke[2] and Poser.[3] The goal of this review is to summarize available recent data on survival and the rate at which disability develops in MS and factors which may predict outcome. Special attention will be paid to methodologic difficulties so as to define strategies to improve validity of natural history studies.

Methodology

Studies of natural history should attempt to identify a cohort close to the onset of illness ("inception cohort") and provide longitudinal follow-up data over a duration appropriate to the expected time course over which the disease evolves. The requirements of such studies are discussed by Sackett.[4] Several problems, some unique to MS, complicate study design: difficulties identifying patients from onset of MS; bias toward severe and unusual cases in tertiary centers that gather and report data on natural history; slow evolution of disease; loss of institutionalized patients to follow-up; uncertainty as to the optimum parameter to study so as to reflect outcome.

Sample Size & Ascertainment

A summary of the populations studied in existing series is presented in Table 1. Earlier studies[5-7] were largely clinic based and included mixtures of inpatients and outpatients. S. Poser's study[8] clearly showed the expected bias toward rapid rate of progression of disability in a hospital based series compared to a community based series.

Prospective studies are unrealistic as patients often do not seek medical attention at the time of their first symptoms. It is almost inevitable that the most benign cases will be missed. Asymptomatic cases are found at autopsy[9] and patients with a single attack are not reliably diagnosed. Patients are generally heterogenous with respect to duration of illness and disability when first evaluated at our clinic. Two strategies that minimize ascertainment bias are (1) separately evaluating patients seen

From the Department of Clinical Neurological Sciences, University of Western Ontario, London
Received October 14, 1986. Accepted in final form February 22, 1987.
Reprint requests to: Dr. G.C. Ebers, Department of Clinical Neurological Sciences, University Hospital, P.O. Box 5339, London, Ontario, Canada N6A 5A5

Table 1: Population Size & Patient Ascertainment

Author	Location	Year	Population Size	Diagnostic Certainty	Ascertainment			Geographically* Based	Mean Time From Onset to Ascertainment (years)
					H	C	P		
Thompson[23]	Dublin	1986	290	DP	+	+			NR
Visscher[12]	Los Angeles County,	1984	941						
Detels[14]	California & King &	1982	886	DP			+	+	<10
Clark[13]	Pierce Counties, Washington	1982	834						
Verjans[27]	Belgium	1983	200	D		+			NR
Patzold[20]	Hanover, Germany	1982	102	NR		+			3**
Poser[8,28]	Gottigen, Germany	1982	2058	DPP	+(1837)	+(221)		+(221)	NR
Broman[24]	Gothenburg, Sweden	1981	312	DPP		+		+	NR
Confavreux[15]	Lyon, France	1980	349	DPP		+		+	NR
Kurtzke[11]	USA	1977	527	DP			+ (Army Discharges)		3**
Percy[35]	Rochester, Minnesota	1971	67	DP		+			NR
Gudmundsson[19]	Iceland	1971	104	DPP			+	+	12
Fog[21]	Copenhagen, Denmark	1970	73	D		+			NR
Leibowitz[16,17,18]	Israel	1970 1964	266	DPP			+	+	11.5
Panelius[22]	Turku District, Finland	1969	146	DP			+	+	5
McAlpine[6,10]	London,	1961	241			+			<3
	England	1952	675		+	+			NR

* According to author, supported or unsupported, most cases in the area surveyed were identified

** Estimated from available data

H = Hospital; C = Clinic; P = Prevalence Survey; D = clinically definite; DP = clinically definite & probable; DPP = clinically definite, probable & possible; NR = not recorded

from onset (2) conducting geographically based studies, wherein all cases in a community are identified regardless of severity.

The first approach has been used by McAlpine,[10] Kurtzke[11] and by the UCLA group.[12-14] The latter group restricted their study to patients with onset between 1960 and 1970, so as to avoid inclusion of those with long survival to the exclusion of others who had died before the prevalence date in 1970. Duration from onset to ascertainment in the series surveyed varies from 2-12 years. The longer the time the greater the potential bias as more severe or rare fatal cases could have been missed.

The second approach, ie. a complete community survey, has been used by several groups with varying degrees of verification. These investigators include the UCLA group for three U.S.A. west coast counties,[12-14] Confavreux[15] for Lyon, France, Leibowitz[16-18] for Israel, and Gudmundsson[19] for Iceland. Kurtzke's study of World War II veterans[11] is unique in that the degree of ascertainment was high in the chosen sample, as compensation was provided for veterans with this diagnosis. The interval from onset to ascertainment was short. The study was limited, however, by the unavoidable restriction to otherwise healthy young males.

Several studies[15,20] have included patients treated with immunosuppressive drugs which could have potentially altered outcome.

Follow-up

The key elements are as follows: 1) adequate duration 2) standardized recording of data 3) evaluation at a point of relative clinical stability rather than at the time of an exacerbation 4) adequate tracing of cases so that patients are not lost for reasons arising from the outcome of illness (death or institutionalization).

A prospective study of an inception cohort has not been done. In the few prospective studies[12-14,20] patients are heterogeneous in duration of illness and disability at time of entry. In the remainder, follow-up can be classified as longitudinal[15,19,21] or cross sectional.[6,11,16,17,22,23] In the former, fluctuations unrelated to fixed disability generally do not have a major impact, while these can cause significant problems with interpretation in the latter, especially when data are extracted from traditional records. Kurtzke[11] reported that of 34 patients with severe disability at diagnosis, 11.8% had only mild disability at 10 years and 32.4% had moderate disability. Such improvement

https://doi.org/10.1017/S0317167100026573 Published online by Cambridge University Press

Table 2: Patient Follow-up

	Type of Study			Duration of Follow-up (years)		Duration of** Disease (years)	
	P	L	CS	Mean	Range	Mean	Range
Thompson[23]			+			11.4	
Visscher[12] Detels[14] Clark[13]	+			10			10-20
Verjans[27]			+				2-48
Patzold[20]	+			3.5			
Poser[8,28]							
Epidemiologic		+				12.1	
Hospital			+			10.5	
Broman[24]		+			<20		13-27
Confavreux[15]		+		9			
Kurtzke[11]			+ (multiple points)				10-21
Percy[35]			+				
Gudmundsson[19]		+			14-23	24	
Fog[21]		+		10*		20*	
Leibowitz[16,17,18]			+			11.5	
Panelius[22]			+				0-39
McAlpine[10]		+			>10		10-29
McAlpine[6]			+				

** Duration shown is that at the conclusion of follow-up in prospective & longitudinal studies

* Estimated from available data

P = Prospective; L = Longitudinal; CS = Cross Sectional

would be unlikely if the original findings were recorded at a time of clinical stability.

The duration of follow-up varies (see Table 2). In Patzold's prospective study,[20] the mean follow-up was only 3.5 years. Given that the patients studied were at different stages of MS, the results are of limited value. The scales employed were highly sensitive and the fluctuations observed were of questionable significance in relation to ultimate disability. In Kurtzke's study,[11] however, follow-up was at least 10 years and relatively few patients were not traced (24% at 10 years and 38.7% at 15 years). Coupled with a high degree of ascertainment in the target sample and the short interval between onset and ascertainment, this is a very important study.

Measures of Outcome

Measures of outcome must be sensitive yet clinically meaningful and must mirror fixed disability. As survival is only minimally altered by MS (see below), it is not useful as a primary measure of outcome. Similarly, employment status has a weak relationship with disability. Attack frequency is more dependent on such factors as age and duration than on outcome. Most investigators have not found a correlation between attack frequency and disability.[11,20,21,24]

Carefully recorded disability status at a point of relative clinical stability is the most desirable single measure. Several scales have been proposed, but the Kurtzke disability status (KDS) scale,[25] which has recently been extended,[26] is the most sensitive and useful. It is primarily a measure of mobility. It has often been divided by duration to generate a "progression index",[8,27,28] thereby assuming linearity of the KDS. A frequency distribution of disability stratified according to duration[11] is preferable given the ordinal nature of the scale.

MRI may offer a sensitive and objective means of follow-up.[29-33] Recent studies show a correlation between semi-quantitative assessment of lesion severity on MRI and the KDS.[31,32] Others suggest that new lesions may develop without clinical correlates, challenging the significance of our clinical interpretations of disease stability.[29,33] This is reconciled, in part, by the eloquence of the site involved by a plaque. The final concern of both patient and physician is undoubtedly disability, which is best quantitated at the bedside.

The Temporal Course of MS

Survival

Kurtzke[2] has previously reviewed existing mortality data and methods by which survival and mortality can be determined. Mean duration of disease in fatal cases (see Gudmundsson[19] and McAlpine[6]) is misleading as only a small percentage of cases is expected to die of MS. The duration of disease in survivors is dependent on the length of follow-up. Life table analysis has been employed by several authors.[2,24,34,35] Ideally, this involves follow-up of a cohort from onset identifying all deaths; in reality, the available data are subject to the aforementioned biases arising from incomplete ascertainment and follow-up. When compared to an appropriately matched population for age, sex, race, etc., the survival of MS patients as a percent of expected survival has been determined. Data from the series considered are shown in Table 3. These data are consistent with the low mortality rate reported by Gudmundsson[19] who found the mortality rate to be 1.3% per year. Others have reported higher rates of 2% to 4% per year as summarized by Gudmundsson[19] and Leibowitz.[36] Kurtzke[2] corrects his survival data for deaths not attributable to MS to show that MS patients have 75% of normal survival at 25 years. This agrees with data reported by Percy from Rochester, Minnesota.[35] Broman,[24] comparing his population to an age and sex matched Swedish population, finds that his MS patients have 85% of expected survival at 25 years.

Disability

Little information is available on the rate of accumulation of functional disability in MS and virtually none is available on the rate from onset of progressive disease. The only series which provide precise data as to disability indexed to duration of disease are those of Kurtzke,[11] Confavreux,[15] Panelius,[22] and McAlpine and Compston.[6] Of these, ascertainment and follow-up are most complete in Kurtzke's study.

Using the conversion scheme proposed by Detels,[14] the rates at which various levels of disability are reached are summa-

Table 3: Survival in MS Determined by Actuarial Analysis

Years After Onset	Percentage of Patients Surviving 5	10	15	20	25
Broman[24]	99	96	90	85	75
Confavreux[15]	99	96	88		
Kurtzke[2,34]					
uncorrected	96	90	83	74	66
corrected for non-MS related deaths	98	91	85	79	75
Percy[35]	99	98	90	80	74

rized in Table 4 in terms of KDS equivalents. The disparity between the various series can, in part, be accounted for by differences in the scales used. At lower levels of disability (KDS 1-5), the Detels/Visscher, Hyllested and McAlpine scales are insensitive. Also, the KDS scale includes deaths due to MS (KDS 10) unlike the McAlpine and Hyllested criteria. This avoids the potential difficulty in series that show disability only in survivors.[6,22] Paradoxically, the percentage of patients severely disabled declines with higher mortality.

Considerable disparity among the series is evident. McAlpine's low estimate of the percentage of patients with disability equivalent to KDS 8 in his 1952 series[6] likely reflects his clinic and hospital based ascertainment, which is prone to incomplete follow-up of patients with advanced disability. Kurtzke's veteran series[11] and Panelius' population based series[22] suggest that 29% and 14% of patients, respectively, followed 15 years from onset, are at or beyond the equivalent of KDS 8 (bedridden). With the exception of Panelius' series, those cited suggest that 50-60% of MS patients 15 years from onset have not reached KDS 6 (aids required for ambulation).

With the degree of accuracy and precision that is necessary to plan efficient clinical trials, more precise data, expressed in terms of the expanded disability status scale of Kurtzke,[26] are desirable.

Attack or Relapse Rate

The relapse rate varies with age, being higher in the younger patient.[20,24] It also depends on the duration of disease, decreasing with time from onset, and is independent of the clinical course, whether progressive or stable.[6,10,20,22,24] Calculation of relapse rate by averaging total number of relapses divided by patient years of a population at different stages of MS is, therefore, of limited value. Some accept nonspecific symptoms or brief fluctuations in neurologic dysfunction as attacks; others require that some degree of remission occur. Furthermore, retrospective data consistently show lower rates than prospective data.[20,21] Comparisons among series are, therefore, difficult. The definition of an attack should adhere to established criteria.[37,38] However, this definition is to some extent arbitrary. Broman[24] distinguishes an episode of worsening disability, intermediate in rate of onset and duration between an attack and progression. He refers to such episodes, which can last months before stability is reached as "periods". While this term may be meaningful, it is difficult to quantitate. Data on the attack rate from retrospective series, especially when gleaned from conventional medical charts, are of limited accuracy.

Representative published figures for attack rate are presented in Table 5. Variation of an entire order of magnitude from 0.14/year[19] to 1.1/year[20] exists. Differences are likely accounted for by differences in definitions, the prospective nature of the studies with the highest relapse rates and the frequency with which patients were assessed in the retrospective series. In Gudmundsson's series,[19] the low rate may well reflect the long duration from onset to ascertainment; in our experience, patients seen for the first time generally underestimate the frequency of their attacks in the early years of their disease.

Parameters Predictive of Outcome

The Early Clinical Course

If the early clinical course of MS were predictive of later outcome, patients with an unfavourable prognosis could be better selected for study of therapeutic interventions which entail risk. The onset of progressively worsening disease is generally acknowledged to carry a poor prognosis;[11,15,18,27,28] however, this point of general agreement is limited in practical application because transition from relapsing to progressive disease can only be determined after progression occurs. Kurtzke[11] points out that "this is an observation after the fact and not a prognostic or predictive criterion". It would be desirable to determine prognosis in the patient at a low level of disability. Two features that could be considered are the early development of disability and the early relapse rate.

Kurtzke[11] claims that the disability status at 5 years from diagnosis is predictive of the disability status at 10 years and 15 years. Only 7.47% of those with mild disability at 5 years after onset were severely disabled (KDS 6-10) at 10 years after diagnosis and only 11.4% were severely disabled at 15 years. Given that 37% and 46% of all patients with duration 10 and 15 years respectively in Kurtzke's series had progressed to KDS 6 or beyond (see Table 4), this provides a significant refinement in prognosis for the 20% who had only mild disability at 5 years. For the majority of patients with moderate disability (KDS 3-5) at 5 years, roughly 50% remained within that category at 15 years and 50% became worse with severe disability (KDS 6-10). Thus, the predictive value of moderate disability at 5 years which affected over 50% of cases was no better than inferences from the entire group.

Table 4: Disability in MS as a Function of Duration +

	Percent of Patients at or Beyond											
	KDS 3 (Moderate Disability)				KDS 6 (Assistance Required For Walking)				KDS 8 (Bedridden)			
AUTHOR	C*	K*	P	M	C*	K*	P	M	C*	K*	P	M
Years From Onset												
5		82			8	25	42	18		8	4	<1
10		77			25	37	68	32		17	9	<1
15		82			40	46	76	32		29	14	<1

+ In equivalents of the Kurtzke Disability Score (KDS) according to the conversion scheme of Detels[14]

* Deaths due to MS (KDS 10) Included

C = Confavreux;[15] K = Kurtzke;[11] P = Panelius;[22] M = McAlpine[6]

Table 5: Attack Rate in MS

	Attack Rate Per Person-Year				
Years From Onset	1	2	5	10	Average
Patzold[20]					
Prospective	1.8	1.3	1.0	0.9	1.1
Retrospective	1.8	1.2	0.8	0.5	
Gudmundsson[19]					0.14
Fog[21]					
Prospective					0.56
Retrospective					0.35
Leibowitz[16,17,18]					0.39 (first 5 years)
Panelius[22]					0.26
McAlpine[6]	1.23	0.42	0.35	0.30	0.39

https://doi.org/10.1017/S0317167100026573 Published online by Cambridge University Press

Detels[14] concluded that the level of disability in a group of patients examined in 1972 predicted which patients would be worse when they were re-evaluated in 1979. However, the duration from onset of symptoms at the time of initial evaluation in 1972 varied by up to 10 years. Differences in the degree of progression were not stated, and the percentage of patients that worsened was no greater than twofold in the group with advanced disability compared to those with lesser degrees of disability. Once again, the percentage that worsened was greatest in patients with intermediate levels of disability (walking with aids), and of these, approximately 50% were classified as being worse and 50% were not.

The attack rate is, as previously noted, subject to variation in definition. While McAlpine[10] suggests that a low relapse rate, particularly after the second year of disease, is associated with benign disease, this is not the experience of most investigators. Confavreux[15] found that the mean duration between the first and second relapse is approximately 6 years in "benign" and "intermediate" cases (defined by the rate at which disability developed), compared to 0.9 years in "hyperacute" and 2.4 years in "acute" cases; however, the number of relapses was greater for benign than for more malignant MS. Thompson[23] has also described a significant association between short first remission (less than 1 year) and increased risk of progressive disease. Both Patzold and Pocklington[20] and Fog and Linnemann[21] found no correlation between the rate of disease progression and relapse rate, although follow-up in the former was short, and in both studies progression was indexed only to the period of observation rather than to the entire course from onset. Kurtzke[11] found no association between attack frequency in the first five years and disability status at 10 or 15 years; however, the study was retrospective and the attack rate was predictably low.

In summary, it appears that minimal disability at 5 years from onset is clearly favourable, but intermediate disability at that time is of uncertain significance. No conclusion is possible as to the predictive value of the relapse rate until this parameter is rigorously defined and analyzed at a consistent point in a patient's course.

Demographic and Clinical Features

Several investigators have sought to determine if various clinical and demographic factors have prognostic significance (see Table 6). Chief among these have been the age of onset, sex, and initial symptoms. These parameters are not independent of one another; for example, the older patient often presents with pyramidal symptoms and pursues a more rapid course.[39]

Many investigators fail to show a sex difference,[12,15,23,27] although others disagree.[6,14,18,22] Most find a worse prognosis in patients who are older at onset; however, the principal difference appears to be between patients less than or greater than 40 years at onset.[12,18,28] Few show significant differences in outcome according to age at onset in patients younger than 40 years[11,28] with the exception of Thompson[23] who recently reported a significant correlation between age and "benign" MS (KDS ≤3 at 10 years). There is poor agreement regarding the quantitative, if not qualitative prognostic value of initial clinical findings. Several authors find optic neuritis to be favoura-

Table 6: Clinical & Demographic Predictive Factors*

Variable	Author	Relatively Favourable	No Influence	Relatively Unfavourable
Sex	Thompson[23]		+	
	Visscher[12]		+	
	Detels[14]	Female		Male
	Verjans[27]		+	
	Confavreux[15]		+	
	Leibowitz[18]	Male		Female
	Panelius[22]	Female		Male
	McAlpine[6]	Female		Male
Age At Onset (years)	Thompson[23]	young age		
	Visscher[12]	<40		>40
	Verjans[27]	<31		>31
	Poser[28]	<39	<20 vs 20-29 vs 30-39	>39
	Kurtzke[11]		+	
	Leibowitz[18]	<40		>40
	Gudmundsson[19]		+	
	McAlpine[10]		+	
Initial Symptoms/Signs	Thompson[23]			Motor
	Visscher[12]	ON, Sensory		Motor, Incoordination
	Poser[28]	ON		
	Confavreux[15]		+	
	Kurtzke[11]		BS, Sensory, Sphincter	Motor, Cerebellar
	Leibowitz[18]	Motor, Sensory	ON	Cerebellar
	Fog[21]		+	
	Gudmundsson[19]		ON	Motor, Motor + Sensory
	McAlpine[10]	ON, BS, Sensory		Pyramidal, Cerebellar

* According to Authors' Conclusions
ON = Optic Neuritis; BS = Brainstem

ble.[10,12,28] Pyramidal (motor) and cerebellar findings are generally acknowledged to be unfavourable.[10,11,12,18,23] The presence of multiple symptoms at onset predicts a poor prognosis according to some.[10,18] Some find that concomitant sensory symptoms have a favourable influence on prognosis compared to motor symptoms alone.[12]

Kurtzke[11] found no difference in his veteran series depending on latitude or rural/urban residence at induction. Visscher,[12] however, found a significantly worse outcome in patients, comparably ascertained, in Los Angeles County compared to those in King and Pierce counties in Washington state. This could be due to either environmental (ie. climate) or host (ie. genetic) differences.

The potential influence of HLA type on prognosis is addressed by several authors[40-43] with discrepant conclusions.

Conclusion

Accepting inherent methodologic limitations, a consensus statement from available data follows. The outcome of MS is highly variable. The disease will most often pursue a remitting course initially, but progressive development of disability to the extent of requiring aids for ambulation or worse occurs in just less than 50% within 15 years of diagnosis. Relapse rate has a poor relationship with the rate of disease progression. Lack of disability at 5 years strongly points to a future (for the ensuing 10 years) benign course in the US veteran study.[11] In the majority of patients, however, who develop moderate disability within 5 years, it is difficult to predict if the disease will progress to severe disability over the next 10 years beyond the 50% risk noted above.

Studies of the natural history of MS will continue to be confounded by difficulty identifying patients at onset and ensuring complete follow-up. Nonetheless, guidelines have been suggested against which methodology can be assessed to determine the reliability of data. Kurtzke's veteran study[11] provides important disability information on a uniquely ascertained group of patients seen over a long period of observation; however, the means of follow-up lack the accuracy of standardized longitudinal clinic information. The challenge for clinic based studies is, therefore, improvement in ascertainment and tracing of patients. With widespread use of experimental therapies, the natural history of MS may have to be determined from data collected to date.

References

1. Noseworthy JH, Seland TP, Ebers GC. Therapeutic trials in multiple sclerosis. Can J Neurol Sci 1984; 11: 355-62.
2. Kurtzke JF. Symptomatology of Multiple Sclerosis. *In:* Vinken PJ, Bruyen GW, Klawans HL, eds. Handbook of Clinical Neurology. Vol 9, Amsterdam: Elsevier Science Publishing Co., 1971: 186-216.
3. Poser S. Multiple Sclerosis. An analysis of 812 cases by means of electronic data processing. Berlin: Springer - Verlag, 1978; 54-66.
4. Sackett DL, Haynes RB, Tugwell P. Clinical Epidemiology. A Basic Science for Clinical Medicine. Boston: Little, Brown & Co, 1985.
5. Lazarte JA. Multiple sclerosis: Prognosis for ambulatory and non-ambulatory patients. Assoc Res Nerv Dis Proc 1950; 28: 512-23.
6. McAlpine D, Compston N. Some aspects of the natural history of disseminated sclerosis. Quart J Med 1952; 21: 135-67.
7. Muller R. Studies on disseminated sclerosis with special reference to symptomatology, course and prognosis. Acta Med Scand 1949; Supp 222: 1-214.
8. Poser S, Bauer HJ, Poser W. Prognosis of multiple sclerosis. Results from an epidemiological area in Germany. Acta Neurol Scand 1982; 65: 347-54.
9. Gilbert JJ, Sadler M. Unsuspected multiple sclerosis. Arch Neurol 1983; 40: 535-36.
10. McAlpine D. The benign form of multiple sclerosis. A study based on 241 cases seen within three years of onset and followed up until the tenth year or more of the disease. Brain 1961; 84: 186-203.
11. Kurtzke JF, Beebe GW, Nagler B, et al. Studies on the natural history of multiple sclerosis VIII. Early prognostic features of the later course of the illness. J Chron Dis 1977; 30: 819-30.
12. Visscher BR, Liu KS, Clark VA, et al. Onset symptoms as predictors of mortality and disability in multiple sclerosis. Acta Neurol Scand 1984; 70: 321-28.
13. Clark VA, Detels R, Visscher BR, et al. Factors associated with a malignant or benign course of multiple sclerosis. JAMA 1982; 248: 856-60.
14. Detels R, Clark VA, Valdiviezo NL, et al. Factors associated with a rapid course of multiple sclerosis. Arch Neurol 1982; 39: 337-41.
15. Confavreux C, Aimard G, Devic M. Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients. Brain 1980; 103: 281-300.
16. Leibowitz U, Halpern L, Alter M. Clinical studies of multiple sclerosis in Israel. Arch Neurol 1964; 10: 502-12.
17. Leibowitz U, Alter M, Halpern L. Clinical studies of multiple sclerosis in Israel III: Clinical course and prognosis related to age at onset. Neurology 1964; 14: 926-32.
18. Leibowitz U, Alter M. Clinical factors associated with increased disability in multiple sclerosis. Acta Neurol Scand 1970; 46: 53-70.
19. Gudmundsson KR. Clinical studies of multiple sclerosis in Iceland - a follow-up of previous survey and reappraisal. Acta Neurol Scand 1971; 47 (Suppl 48): 1-53.
20. Patzold U, Pocklington PR. Course of multiple sclerosis: First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand 1982; 65: 248-66.
21. Fog T, Linnemann F. The course of multiple sclerosis in 73 cases with computer designed curves. Acta Neurol Scand 1970; 46 (Suppl 47): 1-175.
22. Panelius M. Studies on epidemiological, clinical and etiological aspects of multiple sclerosis. Acta Neurol Scand 1969; 45 (Suppl 39): 1-82.
23. Thompson AJ, Hutchinson M, Brazil J, et al. A clinical and laboratory study of benign multiple sclerosis. Quart J Med 1986; 58: 69-80.
24. Broman T, Andersen O, Bergmann L. Clinical studies on multiple sclerosis I. Presentation of an incidence material from Gothenburg. Acta Neurol Scand 1981; 63: 6-33.
25. Kurtzke JF. On the evaluation of disability in multiple sclerosis. Neurology 1961; 11: 686-94.
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983; 33: 1444-52.
27. Verjans E, Theys P, Delmotte P, et al. Clinical parameters and intrathecal IgG synthesis as prognostic features in multiple sclerosis. Part I. J Neurol 1983; 229: 155-65.
28. Poser S, Raun NE, Poser W. Age at onset, initial symptomatology and the course of multiple sclerosis. Acta Neurol Scand 1982; 66: 355-62.
29. Noseworthy JH, Paty DW, Ebers GC. Neuroimaging in multiple sclerosis. Neurologic Clinics 1984; 2: 759-77.
30. Johnson MA, Li DKB, Bryant DJ, et al. Magnetic resonance imaging: Serial observations in multiple sclerosis. AJNR 1984; 5: 495-99.
31. Stevens JC, Farlow MR, Edwards MK, et al. Magnetic resonance imaging: Clinical correlation in 64 patients with multiple sclerosis. Arch Neurol 1986; 43: 1145-48.
32. Matias-Guiu J, Sanz M, Gili J, et al. Correlation of MRI with the clinical status of patients with multiple sclerosis. Neurology 1986; 36: 1626.
33. Paty DW, Palmer M, Bergstrom M, et al. Magnetic resonance imaging in multiple sclerosis: Quantitative changes in the size of

lesions over 6 months in the placebo limb of a therapeutic trial. Can J Neurol Sci 1986; 13: 168.
34. Kurtzke JF, Auth TL, Beebe GW, et al. Survival in multiple sclerosis. Trans Am Neurol Assoc 1969; 94: 134-39.
35. Percy AK, Nobrega FT, Okazaki H, et al. Multiple sclerosis in Rochester, Minn. Arch Neurol 1971; 25: 105-11.
36. Leibowitz, U, Kahana E, Alter M. Survival and death in multiple sclerosis. Brain 1969; 92: 115-30.
37. Schumacher GA, Beebe G, Kiblett RF, et al. Problems of experimental trials of therapy in multiple sclerosis; report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann NY Acad Sci 1965; 122: 552-68.
38. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *In:* Poser CM, ed. The Diagnosis of Multiple Sclerosis. New York: Thieme-Stratton Inc, 1984: 225-29.
39. Noseworthy J, Paty D, Wonnacott T, et al. Multiple sclerosis after age 50. Neurology 1983; 33: 1537-44.
40. Engell T, Raun NE, Thomsen M, et al. HLA and heterogeneity of multiple sclerosis. Neurology 1982; 32: 1043-46.
41. Meyer-Rienecker HJ, Wegener S, Hitzschke B, et al. Multiple sclerosis-relation between HLA haplotype A25, B18 and disease progression. Acta Neurol Scand 1982; 66: 709-12.
42. Madigand M, Oger JJ, Fauchet R, et al. HLA profiles in multiple sclerosis suggest two forms of disease and the existence of protective haplotypes. J Neurol Sci 1982; 53: 519-29.
43. Poser S, Ritter G, Bauer HJ, et al. HLA antigens and the prognosis of multiple sclerosis. J Neurol 1981; 225: 219-21.