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RELAPSES AND PROGRESSION OF DISABILITY IN MULTIPLE SCLEROSIS

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ABSTRACT

Background The influence of the patterns of onset of multiple sclerosis and relapses of the disease on the time course of irreversible disability is controversial.

Methods In 1844 patients who had had multiple sclerosis for a mean (\pm SD) of 11 ± 10 years, we determined the time of the clinical onset of the disease, the initial course (relapsing–remitting or progressive) and the subsequent course (relapsing–remitting, secondary progressive, or primary progressive), the times of relapses, the time to the onset of irreversible disability, and the time course of progressive, irreversible disability. We used three scores on the Kurtzke Disability Status Scale (range, 0 to 10, with higher scores indicating more severe disability) as measures of the severity and progression of disability: a score of 4 (limited walking ability but able to walk more than 500 m without aid or rest), a score of 6 (ability to walk with unilateral support no more than 100 m without rest), and a score of 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support). We used Kaplan–Meier analyses to determine the influence of relapses on the time to the onset of irreversible disability.

Results The median times from the onset of multiple sclerosis to the assignment of a score of 4, a score of 6, and a score of 7 on the disability scale were longer among the 1562 patients with a relapsing–remitting onset of disease (11.4, 23.1, and 33.1 years, respectively) than among the 282 patients who had progressive disease from the onset (0.0, 7.1, and 13.4 years, respectively; $P < 0.001$ for all comparisons). In contrast, the times from the assignment of a score of 4 to a score of 6 were similar in the two groups (5.7 and 5.4 years, $P = 0.74$). The time course of progressive, irreversible disease among patients with the primary progressive type of multiple sclerosis was not affected by the presence or absence of superimposed relapses.

Conclusions Among patients with multiple sclerosis, relapses do not significantly influence the progression of irreversible disability. (N Engl J Med 2000; 343:1430–8.)

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MULTIPLE sclerosis is the most common chronic disabling disease of the central nervous system in young adults. It affects 1 in 1000 people in Western countries.¹ It is primarily characterized by multicentric inflammation and demyelination, but the role of axonal injury and gliosis increases as the disease evolves.² In most patients the disease begins at about 30 years of age with acute episodes of neurologic dysfunction, followed by periods of partial or complete remission with clinical stability between relapses — the relapsing–remitting phase of the disease. Except in patients with the relapsing–remitting type of multiple sclerosis, this phase is usually followed by progressive clinical disability, with or without superimposed relapses and remissions.^{3–5} In a minority of patients, the disease is progressive from the beginning, although there may be superimposed relapses and remissions. Therefore, neurologic disability may result from relapses with incomplete remissions, progression of the disease, or both.

Since 1993, two drugs — interferon beta and glatiramer acetate — have been identified as disease-modifying treatments.^{6–10} These drugs reduce the frequency of relapses by about one third but are less effective in slowing the progression of disability.^{8–10} The objective of this study was to determine the influence of acute relapses on the rate of progression of irreversible disability in patients with multiple sclerosis.

METHODS

Patient Population and Data Collection

Patients were identified through the Lyons multiple sclerosis data base.³ This computerized surveillance system was established in 1976 and includes all patients with a diagnosis of multiple sclerosis who were examined at least once at the Clinique de Neurol-

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ogie in Lyons, France. This clinic has served as the referral center for multiple sclerosis for the city of Lyons and the Rhône-Alpes region since 1976. Decisions regarding diagnostic tests and treatments for individual patients were made by referring neurologists or neurologists in the clinic, or both, according to accepted guidelines. Relapses were usually treated with glucocorticoids. Since the late 1960s, azathioprine and cyclophosphamide have been used to treat multiple sclerosis. Azathioprine is administered mainly during the relapsing–remitting phase of multiple sclerosis and after the third relapse, and it is usually stopped when the disease becomes progressive. Cyclophosphamide therapy is used only in severe cases or during the progressive phase of the disease. A single, intense course may be given, or long-term treatment may be given, but it usually lasts no longer than 12 months. Since the early 1990s, methotrexate has been used, usually for no more than 12 months, in some patients with the secondary progressive type of multiple sclerosis.

Each case report in the data base includes identifying and demographic data, medical history, key episodes in the course of the disease (relapses, onset of progressive disease, and onset of irreversible, progressive disability), results of laboratory and electrophysiologic tests, neuroimaging data, and treatment. Data are entered retrospectively when the patient is first seen at the clinic and at each follow-up visit, usually on a yearly basis. Since 1990, data have been recorded on the standardized computerized forms designed for the European Database for Multiple Sclerosis.¹¹ New data are automatically compared with older information, and any inconsistencies are identified. The confidentiality of the data is maintained in accordance with the recommendations of the French Commission Nationale de l'Informatique et des Libertés. All patients gave informed consent to have their data included in the data base.

Definition of Cases

By April 1997, 2021 patients had been included in the data base. Multiple sclerosis was diagnosed according to the classification of

Poser et al.¹² This classification scheme relies on three criteria: dissemination of lesions in time (there must be at least two distinct neurologic episodes in the course of the disease); evidence of spatial dissemination of lesions in the central nervous system, provided by clinical findings or magnetic resonance imaging, computed tomography, or testing of evoked potentials; and quantitative or qualitative abnormalities of immunoglobulins in the cerebrospinal fluid. Cases are considered clinically definite when the first two criteria are met, regardless of the results of cerebrospinal fluid tests; laboratory-supported definite cases meet the first and third criteria or the second and third criteria; clinically probable cases meet the first criterion or the second criterion; laboratory-supported probable cases meet the third criterion; and possible cases do not fulfill any of the criteria but are characterized by neurologic abnormalities that are compatible with the diagnosis of multiple sclerosis.

Assessment of Patients

A relapse of multiple sclerosis was defined as the occurrence, the recurrence, or the worsening of symptoms of neurologic dysfunction that lasted more than 24 hours and that stabilized or eventually resolved either partially or completely. Fatigue alone and transient fever-related worsening of symptoms were not considered relapses. Symptoms that occurred within a month after the initial symptoms of relapse were considered to be part of the same episode.

The onset of progressive disease was defined as a continual worsening of symptoms and signs for a period of at least six months, with or without superimposed relapses.¹³ Once progression has developed, its course is continuous, although occasional plateaus and temporary minor improvements may occur.⁵

Neurologic disability was assessed at each visit to the clinic with use of the Kurtzke Disability Status Scale,¹⁴ which is based on the results of a neurologic examination and the patient's ability to walk. Scores can range from 0 (no neurologic abnormality) to 10 (death from multiple sclerosis). We focused on scores that could

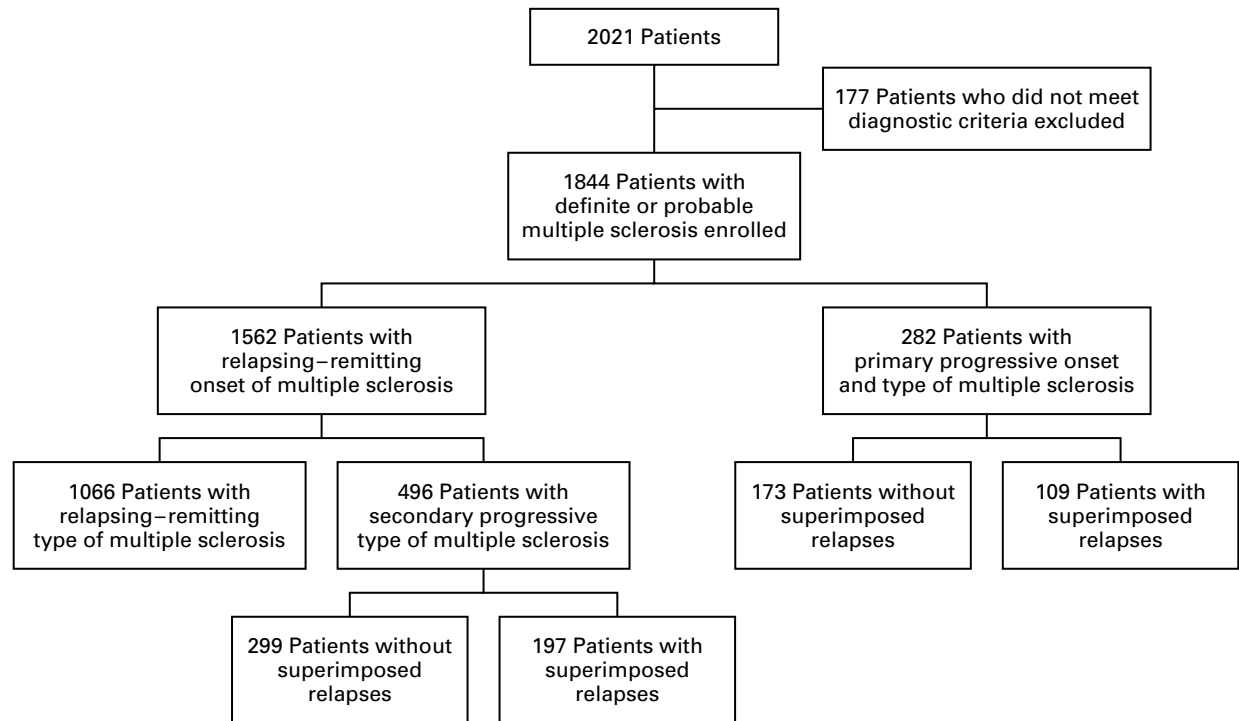


Figure 1. Overall Course and Type of Multiple Sclerosis in the Study Patients.

be easily determined retrospectively: scores of 4 (limited walking ability but able to walk without aid or rest for more than 500 m), 6 (ability to walk with unilateral support no more than 100 m without rest), and 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support). Disability was defined as irreversible when a patient had had a given score for at least six months, excluding any transient worsening of disability related to relapses.

Statistical Analysis

Survival was estimated according to the Kaplan–Meier method, and the log-rank test was used for univariate analyses. The end point was the time to irreversible disability, as indicated by a score of 4, 6, or 7 on the Kurtzke Disability Status Scale. All computations were performed with the use of SPSS software for Windows (version 9.0).¹⁵

RESULTS

Characteristics of the Patients

Of the 2021 patients who were potentially eligible for the study, 170 were excluded because they had possible cases according to the classification of Poser et al.¹² and 7 were excluded because their initial symptoms were unknown (Fig. 1). The base-line characteristics of the remaining 1844 patients with a definite or probable diagnosis of multiple sclerosis are given in Table 1.

A total of 903 patients (49 percent) had received one or more drugs for multiple sclerosis. The most widely used treatment was azathioprine (given to 820 patients), followed by cyclophosphamide (given to 78), interferon beta (given to 72), methotrexate (given to 60), and mitoxantrone (given to 18). As compared with the patients who had not received such drugs, the treated patients had a higher frequency of relapses and a more severe initial course of the disease, findings that presumably reflect a selection bias with respect to the use of drug therapy. Treatment status did not affect the results of our analyses. However, it should be noted that the only treatment with proven efficacy is interferon beta, and the first of these interferons, interferon beta-1b, was not available in our area until February 1996. Moreover, the treatment regimens were heterogeneous, and treatments were usually given for fairly short periods relative to the overall duration of the disease in a given patient.

Initial Course of Multiple Sclerosis and Time to Onset of Irreversible Disability

A total of 1562 patients (85 percent) had relapsing–remitting disease initially, whereas 282 patients (15 percent) had progressive disease. In the entire group of 1844 patients, the median time from the onset of multiple sclerosis to the assignment of a score of 4 on the Kurtzke Disability Status Scale was 8.4 years (95 percent confidence interval, 7.8 to 9.6). The median time from onset of multiple sclerosis to the assignment of a score of 6 was 20.1 years (95 percent confidence interval, 18.1 to 22.5), and the median time from the onset of disease to the assignment of

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1844 PATIENTS WITH MULTIPLE SCLEROSIS.*

CHARACTERISTIC	VALUE
Sex — no. (%)	
Male	657 (36)
Female	1187 (64)
Age at onset of multiple sclerosis — yr	
Mean	31 ± 10
Median	30
Range	5–67
Initial symptoms — no. (%)	
Isolated optic neuritis	335 (18)
Isolated brain-stem dysfunction	159 (9)
Isolated dysfunction of long tracts	964 (52)
Combination of symptoms	386 (21)
Course at onset of multiple sclerosis — no. (%)	
Relapsing–remitting	1562 (85)
Progressive	282 (15)
Time from onset of disease to initial clinic visit — yr	
Mean	6 ± 8
Median	3
Range	0–53
Kaplan–Meier estimate of time from onset of disease to second neurologic episode — yr	
Mean	6
Median	2
Range	0–63
Duration of multiple sclerosis — yr	
Mean	11 ± 10
Median	9
Range	0–63
Type of multiple sclerosis — no. (%)	
Relapsing–remitting	1066 (58)
Secondary progressive	496 (27)
Primary progressive	282 (15)
Diagnosis — no. (%)†	
Clinically definite	1125 (61)
Laboratory-supported definite	251 (14)
Clinically probable	365 (20)
Laboratory-supported probable	103 (6)

*Plus–minus values are means ± SD.

†The diagnoses were classified according to the method of Poser et al.¹²

a score of 7 was 29.9 years (95 percent confidence interval, 25.1 to 34.5). The median interval from the onset of disease to the assignment of each of these scores was significantly longer ($P < 0.001$ for each comparison) in the group of patients with a relapsing–remitting onset of disease than among those who had progressive disease at onset (Table 2 and Fig. 2).

Initial Course of Multiple Sclerosis and the Time Course of Progressive, Irreversible Disability

Among the 1844 patients, 1026 patients (56 percent) reached the end point of a score of 4 on the Kurtzke Disability Status Scale during follow-up. In this group, the median time from the assignment of a score of 4 to the assignment of a score of 6 was 5.7 years (95 percent confidence interval, 5.0 to 6.3). The median time from the assignment of a score of 4 to the assignment of a score of 7 was 12.1 years

TABLE 2. KAPLAN–MEIER ESTIMATES OF THE MEDIAN TIME FROM THE ONSET OF MULTIPLE SCLEROSIS TO THE ONSET OF IRREVERSIBLE DISABILITY AMONG 1844 PATIENTS WITH MULTIPLE SCLEROSIS, ACCORDING TO THE INITIAL COURSE.*

VARIABLE	RELAPSING–REMITTING ONSET			PROGRESSIVE ONSET			P VALUE†
	NO. OF PATIENTS (N=1562)	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	NO. OF PATIENTS (N=282)	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	
			%			%	
Time from onset of multiple sclerosis to assignment of a score of 4	1562	11.4 (10.5–12.3)	52	282	0.0	4	<0.001
Time from onset of multiple sclerosis to assignment of a score of 6	1562	23.1 (20.1–26.1)	73	282	7.1 (6.3–7.9)	40	<0.001
Time from onset of multiple sclerosis to assignment of a score of 7	1562	33.1 (29.2–37.0)	82	282	13.4 (11.0–15.9)	64	<0.001
Time from assignment of a score of 4 to assignment of a score of 6	755	5.7 (4.9–6.4)	44	271	5.4 (4.3–6.6)	38	0.74
Time from assignment of a score of 4 to assignment of a score of 7	755	12.1 (10.0–14.2)	63	271	12.0 (10.1–13.9)	62	0.70
Time from assignment of a score of 6 to assignment of a score of 7	426	3.3 (2.8–3.9)	37	169	4.0 (2.9–5.1)	42	0.48

*The Kurtzke Disability Status Scale was used to determine the extent of disability.¹⁴ On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a score of 4 or more for at least six months, excluding any transient worsening of disability related to relapses. CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡Data on patients who had not reached an end point were censored at the time of the last clinic visit.

(95 percent confidence interval, 10.3 to 13.9). Similarly, 595 patients (32 percent) reached the end point of a score of 6. In this group, the median time from the assignment of a score of 6 to the assignment of a score of 7 was 3.4 years (95 percent confidence interval, 3.0 to 3.8). The median times required for each of these changes to occur were similar whether the disease was initially relapsing–remitting or progressive (Table 2 and Fig. 2).

Effect of Superimposed Relapses during the Progressive Phase on the Time Course of Progressive, Irreversible Disability

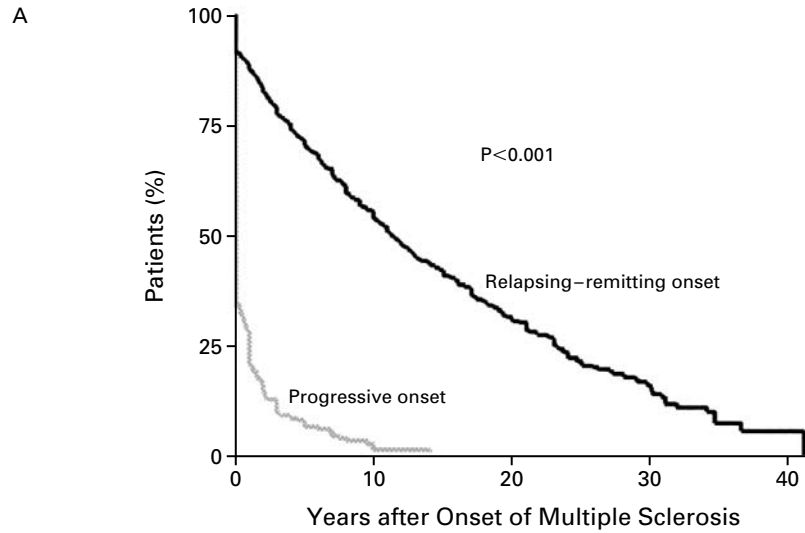
Among patients with the secondary progressive type of multiple sclerosis, the median time from the assignment of a score of 4 on the Kurtzke Disability Status Scale to the assignment of a score of 6 was not influenced by the presence or the absence of superimposed relapses (Table 3 and Fig. 3). In contrast, the median time from the assignment of a score of 4 to a score of 7 and from a score of 6 to a score of 7 was longer among patients with the secondary progressive type who had superimposed relapses than among patients with this type of multiple sclerosis who did not have superimposed relapses (Table 3). Among patients with the primary progressive type of

multiple sclerosis, the median time from the assignment of a score of 4 to a score of 6 or 7 or from a score of 6 to a score of 7 was not influenced by the presence or the absence of superimposed relapses (Table 3 and Fig. 3).

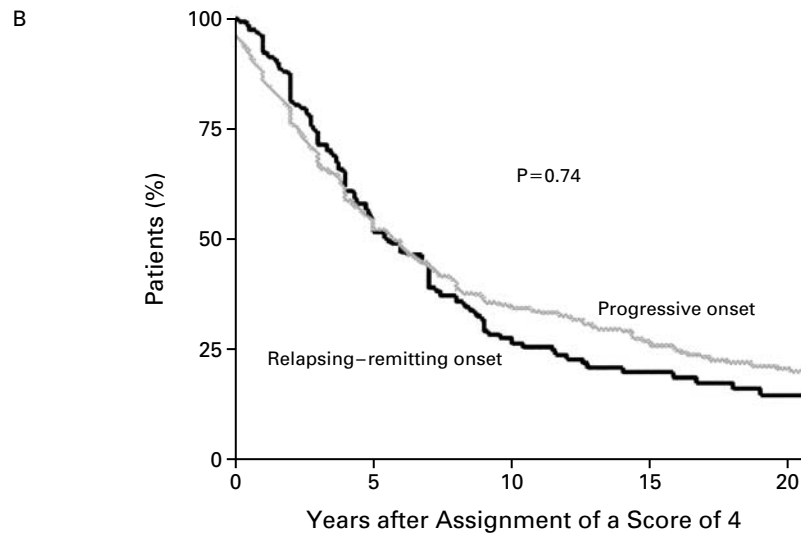
DISCUSSION

In this observational study of the natural history of multiple sclerosis, we found that irreversible disability occurred sooner in patients in whom the disease was progressive from its onset than in those in whom the onset was relapsing–remitting. In contrast, once irreversible disability occurred, the time course of progressive disability was similar in the two groups. In addition, the time course of progressive, irreversible disability among patients with the primary progressive type of multiple sclerosis was not significantly influenced by the presence or absence of superimposed relapses. Among patients with the secondary type of multiple sclerosis (which occurs after a relapsing–remitting phase), the time course of the progressive phase of the disease was longer among patients who had superimposed relapses than among those who did not have superimposed relapses.

The Lyons multiple sclerosis data base is probably among the largest and oldest of such registries. Data

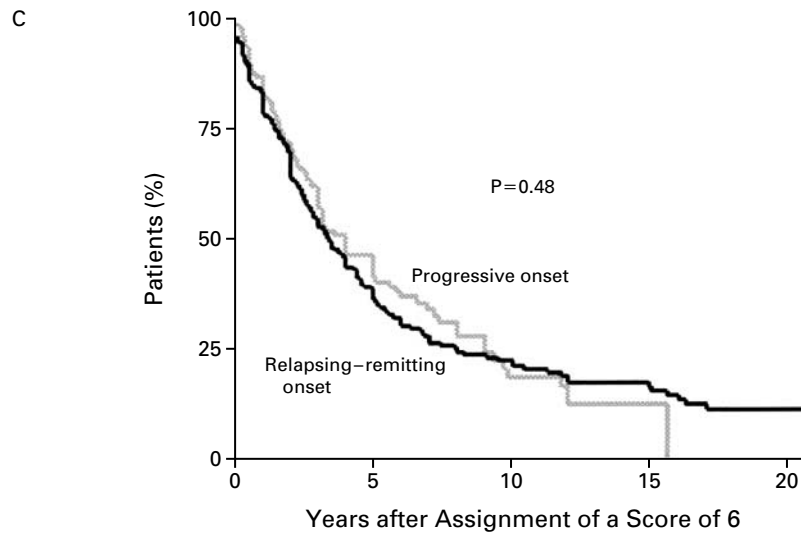


No. AT RISK					
Relapsing-remitting onset	1562	479	116	22	1
Progressive onset	282	2	0	0	0



No. AT RISK					
Relapsing-remitting onset	755	255	114	54	27
Progressive onset	271	103	36	18	10

Figure 2. Kaplan–Meier Estimates of the Time from the Onset of Multiple Sclerosis to the Assignment of a Score of 4 on the Kurtzke Disability Status Scale (Panel A), the Time from the Assignment of a Score of 4 to a Score of 6 (Panel B), and the Time from the Assignment of a Score of 6 to a Score of 7 (Panel C) among 1844 Patients with Multiple Sclerosis, According to the Initial Course.



No. AT RISK					
Relapsing-remitting onset	426	93	31	15	4
Progressive onset	169	41	9	1	0

TABLE 3. KAPLAN-MEIER ESTIMATES OF THE MEDIAN TIME COURSE OF PROGRESSIVE, IRREVERSIBLE DISABILITY AMONG PATIENTS WITH THE PRIMARY OR SECONDARY TYPE OF PROGRESSIVE MULTIPLE SCLEROSIS, ACCORDING TO THE PRESENCE OR ABSENCE OF SUPERIMPOSED RELAPSES.*

VARIABLE	PROGRESSIVE COURSE WITHOUT SUPERIMPOSED RELAPSES			PROGRESSIVE COURSE WITH SUPERIMPOSED RELAPSES			P VALUE†
	NO. OF PATIENTS	MEDIAN TIME (95% CI) yr	PATIENTS WHO DID NOT REACH THE END POINT‡	NO. OF PATIENTS	MEDIAN TIME (95% CI) yr	PATIENTS WHO DID NOT REACH THE END POINT‡	
			%			%	
Secondary progressive type							
Time from assignment of a score of 4 to assignment of a score of 6	292	4.0 (3.1–4.9)	24	191	4.4 (3.9–5.0)	31	0.68
Time from assignment of a score of 4 to assignment of a score of 7	292	7.8 (6.8–8.7)	42	191	10.0 (7.6–12.4)	55	0.04
Time from assignment of a score of 6 to assignment of a score of 7	223	2.6 (2.1–3.1)	27	133	4.3 (3.0–5.7)	38	0.002
Primary progressive type							
Time from assignment of a score of 4 to assignment of a score of 6	163	5.5 (4.5–6.5)	36	108	5.4 (3.3–7.5)	40	0.71
Time from assignment of a score of 4 to assignment of a score of 7	163	12.4 (10.2–14.7)	63	108	11.3 (7.8–14.7)	61	0.65
Time from assignment of a score of 6 to assignment of a score of 7	104	4.0 (2.8–5.2)	44	65	3.6 (2.2–5.0)	38	0.68

*Among the 496 patients with the secondary progressive type of multiple sclerosis, only 483 reached the end point of a score of 4 during follow-up. Among the 282 patients with the primary progressive type of multiple sclerosis, 271 reached this end point. The Kurtzke Disability Status Scale was used to determine the extent of disability.¹⁴ On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a score of 4 or more for at least six months, excluding any transient worsening of disability related to relapses. CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡Data on patients who had not reached an end point were censored at the time of the last clinic visit.

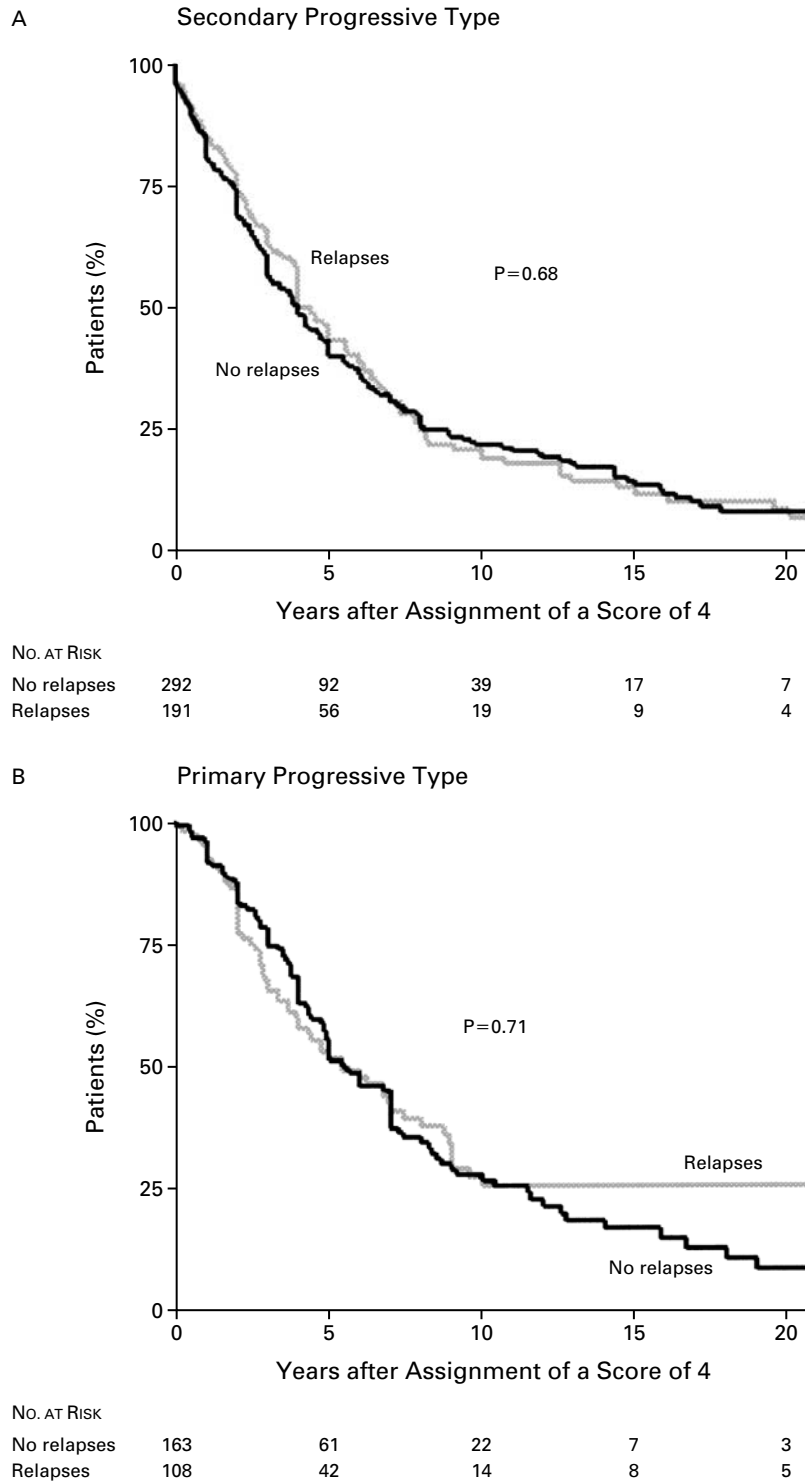


Figure 3. Kaplan–Meier Estimates of the Time from the Assignment of a Score of 4 on the Kurtzke Disability Status Scale to the Assignment of a Score of 6 among the 496 Patients with the Secondary Progressive Type of Multiple Sclerosis (Panel A) and the 282 Patients with the Primary Progressive Type of Multiple Sclerosis (Panel B), According to the Presence or Absence of Superimposed Relapses. Among the 496 patients with the secondary progressive type of multiple sclerosis, only 483 reached the end point of a score of 4 during follow-up. Among the 282 patients with the primary progressive type of multiple sclerosis, 271 reached this end point.

on patients with multiple sclerosis who were referred to and subsequently followed in the clinic are entered in the data base by a group of neurologists who use commonly accepted guidelines and a standardized approach.¹¹ In terms of their demographic characteristics, clinical course, and prognosis, our cohort of patients is similar to those in other major published studies.^{4,16,17}

The first validated disease-modifying drug for multiple sclerosis, interferon-beta 1b,⁶ became available in France in February 1996. Approximately half of our patients have received immunosuppressive drugs — azathioprine, in most cases — for some period of time; none of these drugs have a commonly recognized specific effect on the course of multiple sclerosis.¹⁸

Our results are in accordance with and extend those of other large studies of the natural history of multiple sclerosis. A group of Canadian researchers showed that, as compared with patients with the primary progressive type of multiple sclerosis, patients with the secondary progressive type had a slower onset of disability but a faster progression of the disability.¹⁹ The same group also showed that the survival curves were almost identical for patients with the primary progressive type of multiple sclerosis who had superimposed relapses and patients with the primary progressive type who did not have superimposed relapses with respect to the time from the onset of disease to the assignment of a score of 6, a score of 8, and death.²⁰ Others have reached similar conclusions with respect to the time from the onset of primary progressive multiple sclerosis to the assignment of a score of 6.²¹

Relapses and progression are the two basic clinical phenomena of multiple sclerosis. Relapses are considered to be the clinical expression of acute inflammatory focal lesions disseminated in the central nervous system, whereas progression is considered to reflect the occurrence of demyelination, axonal loss, and gliosis. We found that once a clinical threshold of irreversible disability has been reached (a score of 4 on the Kurtzke Disability Status Scale), the progression of disability is not affected by relapses, either those that occur before the onset of the progressive phase or those that supervene during this phase. The absence of a relation between relapses and irreversible disability suggests that there is a dissociation at the biologic level between recurrent acute focal inflammation and progressive degeneration of the central nervous system. This apparent paradox is consistent with the persistence of the progression of disability in patients with multiple sclerosis despite infection with the human immunodeficiency virus²² or despite suppression of the cerebral inflammation after treatment with a potent antileukocyte monoclonal antibody.²³ It also suggests that agents that have a short-term effect on relapses in patients with multi-

ple sclerosis may not necessarily delay the development of disability in the long term.

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