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# Accumulation of irreversible disability in multiple sclerosis: From epidemiology to treatment

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**Abstract**

There is convincing evidence that neurological relapses in multiple sclerosis (MS) are the clinical counterpart of acute focal inflammation of the central nervous system (CNS) whereas neurological progression is that of chronic diffuse neurodegeneration. The classical view is to consider that MS is an organ-specific autoimmune disease, i.e. that inflammation is the cause of the neurodegeneration. The succession of relapses eventually leads to accumulation of disability and clinical progression results from subclinical relapses. A series of recent observations tends to challenge this classical concept.

Important observations have come from the study of the natural history of MS. In the Lyon MS cohort, accumulation of irreversible disability appeared not to be affected by clinically detectable neurological relapses. This has also been shown to be "amnesic" for the early clinical characteristics of the disease, and essentially age-dependent. Suppressing relapses by disease-modifying agents does not dramatically influence the progression of irreversible disability. Interferons β reduce the relapse rate by 30% and conventional MRI activity by more than 50%. In spite of this effect on inflammation, the effect on disability is only marginal and possibly relapse-reduction-dependent. Administration of Campath-1H to patients with very active disease in terms of frequency of relapses, accumulation of disability and MRI activity, results in a profound, prolonged lymphopenia and the suppression of clinical and MRI activity, but in spite of this, clinical disability and cerebral atrophy still progress. The same experience has been reported with cladribine and autologous haematopoietic stem cell transplantation.

All these observations give support to the fact that relapses do not essentially influence irreversible disability in the long term in MS. They are consistent with what has been shown at the individual level in the 1970s by performing serial quantitative neurological examinations over several years, and with what is currently emerging from early and serial structural brain MRI studies. These breakthroughs have immediate implications for the counselling of patients with MS. They suggest that MS is as much neurodegenerative as inflammatory, and should cause the modification of disease-modifying therapeutic strategies by focussing on the protection and repair of the nervous system and not only on the control of inflammation.


*Keywords:* Multiple sclerosis; Relapses; Progression; Disability; Immunomodulatory drugs

## 1. Introduction

The course of multiple sclerosis (MS) may be looked upon as the interaction between two clinical phenomena, relapses and progression, the latter being defined as a steady worsening of symptoms and signs over a minimum of 6 months [1–3], or even 12 months according to recent definitions [4,5]. It is also an interaction between two biological phenomena in the central nervous system (CNS), i.e. inflammation, which is focal, disseminated, acute and recurrent, and degeneration, which is diffuse, early, chronic and progressive. There is strong evidence that relapses are the clinical counterpart of acute focal inflammation of the CNS [6]. There is also growing evidence that progression is the clinical counterpart of chronic and progressive neurodegeneration [7,8]. One of the central issues with respect to outcome in MS is the mechanism of accrual of irreversible disability [8–10]. It may be the result of relapses with sequelae ("relapse-driven") as well as from progression ("progression-driven"). The question arises about the respective contributions of relapses and progression, and of focal inflammation and diffuse degeneration in this cumulative process. The classical view is to consider MS as an organ-specific autoimmune disease. This

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means that inflammation is responsible for the initiation of the degeneration of the CNS. Does this mean that inflammation is also responsible for the perpetuation and progression of neurodegeneration? In such case, the relapses might be the major cause of the accumulation of irreversible disability in MS.

## 2. Relapses are a major cause of irreversible disability

At first glance this assertion is attractive. Relapses may be an important cause of disability in MS. This is a charcateristic of borderline forms of MS, such as Devic's neuromyelitis optica, transverse myelitis, acute disseminated encephalomyelitis and Marburg disease, although it is precisely because they are so devastating that they are not considered as typical MS. Relapse-driven irreversible disability may also be a feature of more classical cases of MS. Clinicians are familiar with anecdotal cases with a definitive neurological deficit brought about by a relapse. Among the 1562 patients of the Lyon's Natural History Cohort with an relapsing-remitting onset of MS (RRMS), 274 (18%) suffered from an initial relapse with irreversible incomplete recovery as defined by a score of $\geq$3 on the Kurtzke scale; among the 1288 patients with a complete recovery as defined by a DSS score $\leq$2, after the initial relapse, 391 (30%) later experienced incomplete recovery from a subsequent relapse [11]. A detailed analysis of pooled data from 224 patients with RRMS enrolled in the placebo arms of several randomized clinical trials made possible a comparison of EDSS assessments prior to, at the time of, and after a relapse of MS [12]. The baseline EDSS assessment was defined as the most recent one preceding the relapse. Comparing post-relapse and baseline evaluations, the net increase in the EDSS score was $0.27 \pm 1.04$ (mean $\pm$ S.D.; median = 0). This corresponds to 42% of the patients with a $\geq$0.5 and 28% with a $\geq$1.0 EDSS point increase. In this study however, the median time between evaluations performed during and after the relapse was only 63 days (range 32–140 days).

Similarly, the assessment of the possible effect of the degree of recovery from the initial neurological episode, of the time from the initial episode to the second episode and of the number of relapses during the first years of the disease, on the disability accrual process, gives the same results in natural history MS cohorts. Incomplete recovery from the initial episode, a short interval between the first two episodes and a high number of relapses during the first years of the disease are associated with a rapid accumulation of irreversible disability [11,13–15]. Brain MRI studies of cases of MS, with recent onset or of the first neurological episodes suggestive of MS, consistently show tissue destructuration with axonal loss in the acute lesions. Recent pathological studies of MS brain tissue have provided convincing explanations of the causal effect of relapses on the accumulation of irreversible disability. Focal inflammation can indeed lead to focal tissue destruction with demyelination, astrocytic gliosis and, more importantly, axonal transsection [16,17].

## 3. Relapses are not the major cause of irreversible disability

The actual contribution of relapses to disability accumulation is not clear. Inflammation also has some beneficial effects, the best evidence being that remission is the rule following a relapse. Some experimental data have also shown that inflanmation may have a neuroprotective effect [18]. Other evidence comes from the primary progressive forms of MS: progression of irreversible disability occurs without superimposed relapses [19] and without clearcut inflammation as seen pathologically and by MRI. The rate of progression of disability in these cases is similar to that of the progressive-relapsing forms of MS, i.e. the forms with a progressive onset and superimposed relapses [9,20,21].

Instructive observations have been made on pooled data from 313 patients with relapsing-remitting MS enrolled in the placebo arms of two large phase III trials of interferon β-1a [22] and glatiramer acetate [23], assessed at 3-month intervals with a 2-year follow-up [24]. Analyses were performed on the 289 patients with complete 2-year data of EDSS assessments. According to the observed course of their EDSS score throughout the 2 years of follow-up, 29% of the patients could be classified as progressors with confirmation at 3 months but, among these progressors, the EDSS increase was still present in only about half of them at the end of the follow-up period. These results clearly show that an increase in disability confirmed at 3 or even 6 months must not be considered equivalent to an irreversible increase in disability. Lublin et al. [12] also found a $\geq$1.0 1 EDSS point increase relatively to baseline in 28% of their patients at a median of 63 days after a relapse in a similar group of patients. This suggests that, in the available placebo cohorts of RRMS patients, confirmed disability increases were mainly relapse-driven; clearly, a short-term confirmed increase in disability is often relapse-driven and reversible. The issue of long-term irreversible progression of disability is quite different. Lessons from natural history MS cohorts have been informative in this respect. The statistical analysis of 1844 patients of the Lyon Natural History MS Cohort, focused on robust landmarks of disability that could easily be identified by successive neurological assessments as well as by a retrospective interview of the patient whenever necessary. They were DSS 4, defined by walking without aid for a limited distance, exceeding 500 m without rest; DSS 6, walking with unilateral support for a distance not exceeding 100 m without rest; and DSS 7, home restriction, a few steps still being possible with holding on to a wall or furniture but not exceeding 10 m without rest. Disability was defined as irreversible when a definite step had