Relapses are the most florid and defining clinical feature of multiple sclerosis (MS). Their frequency is commonly used as a clinical endpoint in randomized controlled trials, considered as an indicator of the disease activity\(^1\) and a surrogate marker for late disability. In addition, their phenotype (e.g. clinically significant or disabling attacks) influences decisions when initiating or escalating therapies.\(^2\)

Although acute attacks can produce temporary or even permanent loss of function, the development of unremitting disability, occurring during the progressive phase, represents the most feared consequence of the disease, accounting for the bulk of its medical, social and economic impact. Long-term severe disability might result from serial, cumulative exacerbations over time, each contributing to the permanent deficit. However, the relationship between mechanisms underlying relapses and those determining axonal loss, which is the pathological substrate of permanent disability, remains ambiguous.\(^3\) Whether or not relapses, and their phenotype, are an important determinant of the disease outcome is a thorny question, with practical implications for therapeutic strategies. Despite the concept that

the hallmark of effective disease-modifying therapies (DMTs) is the suppression of clinical attacks, preventing the onset of progressive MS and delaying its evolution remain major unmet therapeutic needs.4

In striking contrast with the stereotyped clinical features of the progressive phase, acute exacerbations present with heterogeneous symptoms, resulting from a focal inflammatory involvement of different areas within the central nervous system, which follows a seemingly random distribution. Nonetheless, intriguingly, little is known about the mechanisms governing the frequency of relapses and their severity. Episodic acute attacks are the clinical counterpart of ongoing inflammatory activity, which most of the time remains asymptomatic for unknown biological reasons.5 It is believed that the inflammatory lesion topography determines the phenotype of attacks, but at the individual level the correlation between clinical findings and radiological involvement is poor,6 and the increasing number of subjects incidentally found to have radiological isolated syndrome at least partially contradicts this rather simplistic assumption. Patients' age and sex are important determinants of the phenotypic pattern of relapses, which changes over time. Sensory and optic attacks are more likely to occur among women and at younger age, and their incidence decreases with longer disease duration. Pyramidal, cerebellar and brainstem relapses are more commonly observed among men, at older age and later in the disease course.7

Interestingly, clinical demyelinating events tend to recur in previously affected neurological systems, suggesting that the anatomic distribution of the focal inflammatory activity might be genetically influenced.7 In line with this notion, it has been hypothesized that MS patients may have predetermined disease features and an inherent presenting pattern of relapses. The severity and the degree of recovery from acute exacerbations over time is likely to be similar to the initial demyelinating event, therefore some individuals exhibit a tendency to experience more severe attacks with poor recovery.9 Indeed, the phenotypic features of the onset attack are predictors, albeit modest, of the outcome. Clinical onset with motor, cerebellar or brainstem symptoms, and a poor recovery from the first relapse, associates with a higher risk of attaining moderate disability in shorter time, although it does not affect the late disease evolution.9,10

It is plausible to hypothesize that biological factors, determining when asymptomatic inflammatory activity becomes first clinically evident, affect the long-term outcome. Interestingly, recent cerebrospinal fluid analyses suggest that the first clinical disease expression might not be a random occurrence, but the result of a selective focal damage of the grey matter.11 Therefore, mechanisms underlying early clinical attacks might be closely related to the development of the cortical pathology, which is considered an important determinant of the outcome severity.12 In addition, a large number of early relapses (during the first two and five years from onset) predicts a more rapid disease progression.9,10,13,14 The faster accumulation of disability among patients with high early attack frequency is secondary to the anticipated onset of the progressive phase.14 Although it remains unclear whether the relationship between early frequent exacerbations and late severe disability is causal or associative,15 early focal inflammation might create a pathological substrate which facilitates the clinical emergence of progressive MS. The prognostic relevance of early inflammatory mechanisms is also supported by long-term magnetic resonance imaging data, indicating that the accumulation of focal lesions, occurring during the first five years, predicts the development of disability at 20 years from onset.16 This highlights an early window of opportunity for DMTs to potentially exert their maximum efficacy.

However, observations from natural history cohorts suggest that axonal loss and focal inflammation might dissociate early in the disease course, much before the clinical onset of the progressive phase. In contrast to early attacks, late attacks were shown to exert no significant effect on disease evolution.13,14 Groups with different number of relapses after year 2 and of total relapses before progression took similar times to high disability endpoints.14 These results do not support the widespread belief that permanent severe disability is caused by cumulative attacks over time, and indicate that late relapse frequency is not a reliable marker of the disease activity. Relapse breakthrough during therapy might have different biological significance than attacks among untreated patients, and can associate with an increased risk of accumulating disability in the short term,17 although its impact on the long-term evolution remains uncertain. None of the epidemiological studies and clinical trials have addressed the question of whether the late relapse phenotype influences outcome severity, but any attack occurring while on DMT should be interpreted as lack of adequate disease control, irrespective of its severity.

Incomplete remission from late relapses is a potential mechanism of disability accumulation,18,19 which appears to be strongly influenced by age. Severe attacks are more likely to occur at younger age,5 but by growing older the attack frequency decreases20 and patients have less probability to experience complete recovery.7 Few studies have investigated the effect of incomplete
remission from late relapses on the outcome in the short term. Among 224 patients from placebo arms, aged 35.2 mean years and with a mean Expanded Disability Status Scale (EDSS) score of 2.5, 28% were reported to have had a significant residual deficit (≥ 1 EDSS point) 64 mean days after a relapse. Similarly, in a clinic-based study, among 182 patients with a mean age of 37.6 years, 32.7% reached moderate disability within 127 mean days following an acute attack. Although in both studies secondary progressive patients were excluded, the observation period was too short to reliably ascertain whether the worsening of EDSS was related to the gradual onset of the progressive phase, which is likely to supervene at the age and level of disability characterizing those populations. In addition, complete recovery from relapses can occur even after 12 months, in some cases. Certainly, a proportion of patients can develop moderate disability through relapses (25% in the London, Ontario database), but severe disability (EDSS 6 or more) only rarely results directly from acute attacks.

Are we neglecting the importance of relapse phenotype? There is no indication that late attack frequency and phenotype have any impact on the long-term evolution and on the risk of accumulating severe disability. However, evidence suggests that biological mechanisms occurring in the early stage of the disease and tied to onset of progression are likely to be key determinants of the individual outcome severity. Patients with poor prognosis are distinguished by early adverse features, with distinct relapses phenotypic pattern. Further studies should investigate the potential benefit of early aggressive therapeutic relapse suppression against the occurrence of the progressive course.

Acknowledgements
I would like to thank Dr P. Muraro and Dr R. Nicholas for their valuable comments.

Conflict of interest
Dr Scalfari receives research supports from the UK MS society and received personal compensation for speaking activities from Teva and Genzyme.

Funding
This work was supported by the UK MS society (grant number 975/12).

References
Multiple sclerosis relapse phenotype is an important, neglected determinant of disease-outcome: Commentary

Michael Hutchinson

Thomas Scott, who stimulated this debate, asks: ‘Why has the study of relapse phenotype been so delayed’? Both protagonists agree that relapses in multiple sclerosis (MS) do matter (the subject of a previous debate), so let us get that out of the way. Also there are numerous studies, most notably from the Lyon database, indicating that the phenotype of the onset episode has predictive value in relation to time to progression. Thirdly, both protagonists agree that the frequency of relapses in the first few years (sometimes measured as the time to the first relapse) is important in relation to time to secondary progression and even time to death. Thus, clearly, we all agree that the relapse phenotype is important early in the disease course.

Thomas Scott argues that we are neglecting relapse phenotype later in the disease. He points to evidence that a motor system relapse with poor recovery in the setting of relapsing MS may herald the onset of secondary progression. A similar finding has been noted in another recent study showing that relapses, usually occurring within five years after the onset of the progressive phase, tended to speed up the time to Expanded Disability Status Scale (EDSS) 6.0. The same authors therefore suggest that it would be reasonable to consider continuing immunomodulatory therapy for up to five years after the onset of the progressive phase.

Of course relapses represent only a very small proportion of total disease activity in patients with MS. Other controversies have discussed this ‘iceberg’ effect. It is unsurprising that relapses in the corticospinal pathways tend to speed up the time to reach disability milestones measured by a measure of ambulation, the EDSS. We use this measure in daily practice; this should not mean that sensory relapses and new asymptomatic deep white matter plaques on MRI scanning are irrelevant to the total disease burden in MS and longer-term outcomes.

I would argue that by concentrating on relapse phenotype we ignore our real problem, which is the absence of measures of the ongoing inflammatory burden and the accrual of widespread hidden neuronal and axonal injury. At present we have only the patient report, clinical examination and annual MRI scan to guide therapeutic decisions. Even the clinical examination is imperfect; few neurologists have the time or the resources to perform an adequate cognitive assessment in the clinic. Of course there are academic multidisciplinary clinical centres where neuropsychologists assess patients. The vast majority of patients with relapsing MS in the real world do not have access to adequate cognitive assessment, and thus hidden disease activity is missed.

I will remember a number of patients with optic neuritis as the onset symptom. They had a mild course with infrequent relapses. I reassured them, at 15 years after the onset of the disease, that they had a benign form of