The review by Goodin and Bates in this issue on treating multiple sclerosis (MS) when it might first be heralding is indeed timely for a number of reasons. First, virtually all of the first line current disease modifying drugs (interferon beta and glatiramer acetate) have now been shown to be effective at the stage called ‘CIS’ or the first ‘clinically isolated syndrome’ in reducing the chance of developing a relapse (either clinical or new MRI lesions), although we await word from the nearly completed REFLEX study, which is testing interferon beta-1a 44 mcg three times vs. once weekly. Secondly, these first line agents have been with us for nearly two decades and have failed to demonstrate any significant long-term side effects, with nothing new appearing when used in a CIS population. Thirdly, these same drugs are demonstrating even greater efficacy in recent populations compared with the effects shown in the pivotal studies justifying their approval, an effect that many would suggest is due to starting them earlier in the course of disease, which is in turn due to our improved ability to accurately diagnose MS much earlier. Fourthly, although patients presenting with a CIS syndrome might indeed have a disease other than MS, there are now refined diagnostic algorithms for the work up of such patients to insure that there is “no better explanation” than demyelination due to MS. Lastly, the recent BENEFIT data caught us all by surprise by showing that early initiation of interferon beta-1b to CIS patients delayed disease progression (as measured by the expanded disability status scale (EDSS)) at 3 years compared to a placebo group – a time delay for the group that amounted to a mere 1.33 year head start. Could that short time delay really make that much a difference? What is that telling us about the early period following presentation of disease?

Our stroke colleagues have recognized for years that time is their enemy when it comes to the presentation of the first symptoms of stroke and the implementation of therapy. In fact, even though transient ischaemic attacks (TIAs) were thought to represent minor reversible ischemic events, advanced imaging indicate clear areas of damage. Key to the management of stroke is the early implementation of therapy aimed at preventing recurrence, which in many cases can be as imminent as the first 24 hours following a TIA. When and why disease first presents itself is different in every patient, but it seems that once this does happen, it usually means that recurrence is inevitable, warranting an intervention. Since even in stroke, with a known culprit such as a stenosed carotid, it is difficult to predict where and when it will strike again, or more importantly the extent of the insult, studies have shown a clear path for intervention. Have the CIS studies in MS not shown us the same path?

Goodin and Bates review the rationale for starting treatment after CIS and in particular point out that, even at the earliest stage of presentation, patients are showing signs of irreversible damage in the loss of axons or MRI brain volume. Although there is still some controversy in MS as to what contributes to this damage, overwhelmingly it appears that inflammation is important and medications or treatments aimed at controlling inflammation have been successful at limiting the injury, at least in the early stages. That is because as progressive disease becomes more obvious, inflammation becomes less so and trials attempting to slow progression using the same medications that were successful earlier on have been almost universally ineffective. In contrast to stroke where disease is often in the territory of the diseased blood vessel, in MS the early irreversible damage is often outside the area that is involved (e.g. silent MRI brain lesions in a patient presenting with optic neuritis). Although inflammatory infiltrates come and go, what is left behind is often the loss of axons and neurons, which is believed to be the substrate of disease progression in MS; a loss that may not be clinically manifest until enough accumulates for patients to start showing signs of progression in the absence of attacks (i.e. secondary progressive disease). If we are aware, however, that this loss is amassing even at the CIS stage, is there any reason to delay a treatment that might curb the accumulated damage? If it could be established when the first substantia nigra neurons begin to die as a prelude to idiopathic Parkinson’s disease and there was an intervention that could prevent or slow the process might that not be the ideal time to start it? The answer is obvious, unless there is a ‘down’ side to the treatment.

The side effects of current first line MS therapies can be summarily described as nuisance symptoms with rare significant long-term toxicity. Cost, parenterally administration with occasional injection site reactions and minor laboratory tests for monitoring are the obvious discomforts. So what is the concern about
treating CIS with any of these agents? Could it be that some patients presenting with CIS have another disease? Probably not if experienced neurologists see and assess these patients and apply the type of recommended algorithm\(^3\) to insure that no other disease could explain the signs and symptoms. In the BENEFIT study, not a single patient of the 468 that entered that study turned out to have another disease; furthermore, nearly 90% of patients (originally on placebo) met the McDonald criteria for MS by 5 years\(^7\). Therefore reticence for initiating treatment at CIS can hardly be because we are worried that we might not be treating MS. Could it be that we would be mistakenly committing a patient to long-term therapy when they are destined to a benign course? The reality is that there is no way of knowing who will have such a course at the CIS stage and studies have shown that it is a matter of time before even those patients with established disease who appear to be having a benign course turn for the worse.\(^5\)

So if we are not mistakenly treating another disease, causing undue damage by our treatment, orsubjecting patients to a treatment they may never need because they are destined to a non-disabling disease, why is there any reservation at initiating therapy as soon as MS declares itself? Perhaps we should be looking at our patients who experience a first demyelinating event or CIS like someone who just had a TIA, and the silent lesions on the MRI are akin to the symptomatic carotid plaque. Sure, it is difficult to know when that plaque will throw off material again leading to another event, but nobody is going to wait for that to happen before starting treatment to try and lower those chances. That is because the potential damage that would ensue could be large and disabling. In MS, irreversible damage leading to disability is silently accumulating, even with the first event and continues to do so, even in the absence of symptoms. Maybe we need a lesson from our stroke colleagues to recognize that in MS ‘time is also brain’, only we measure it in terms of weeks or months instead of seconds or minutes.

### References

Mark S. Freedman
University of Ottawa, 501 Smyth Road
Ottawa, Ontario, Canada K1H 8L6
Email: mfreedman@ottawahospital.on.ca