Multiple sclerosis, stress and the rules of evidence

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A crime has been committed. There is an innocent victim and guilt to be assigned. An order to ’round up the usual suspects’ goes out. But only one can be found, and the amnestic eyewitness looks up and down the line-up of one and points a finger. As it happens, the accused looks guilty, has a rap sheet a mile long and is convicted, more on the basis of his track record than anything else. Character witnesses are hard to find for repeat offenders. But there are nagging doubts, not the least of which is that the crime is different from the ones previously on his forensic CV. And neither the investigating officers nor the jury were screened for potential bias.

Recall bias is even possible in prospective cohort studies when exposure status is transient. Finding a significant difference between weekly self-reports before the outcome in question, compared to those completed improperly on the day of or after the outcome, the authors of a study on herpetic eye recurrences (Teschke et al. 2000) concluded, ‘without real-time monitoring of exposure reporting, preservation of the temporal exposure-disease relationship … may be particularly tenuous when transient exposures are investigated longitudinally’. From the same paradigm of recurrent ocular herpes comes even more worrying data (Kip et al. 2001). Here the study design, aimed at examining the role of stress on herpes recurrence, required weekly logs (as in the Buljevac et al. study but only 8-weekly collections were made in the latter). In a thoughtful analysis, the authors divided responses into those filled out at the time of recurrence and those filled out the next week. Disconcertingly, those filled out at the time of herpes recurrence showed no effect of stress, while, amazingly, those filled out the following week and therefore in micro-retrospect showed a significant role for stress. Recall bias, you may take a bow. One is reminded of Max Planck’s dictum that we are at our most vulnerable when others are confirming our views. What the patients thought before the study may be more relevant than suspected.

What about plausibility? The stress is bad concept owes much to Selye’s general adaptation syndrome. However, this had more to do with generalized and prolonged stress and he emphasised the non-specific component that united a variety of stressors. But what to mea-
ure among these? There has to be a difference between the elevated catecholamines in a variety of experimentally unethical stresses and those resulting from exercise. Buljevac and colleagues suggest that stress is producing an exacerbation of a putatively autoimmune disease, whereas much literature suggests it actually diminishes immune function and ergo is blamed for a variety of infectious susceptibilities.

There should be something to measure, even if only semi-quantitatively, to provide some coherence for the role of stress in disease. For example, a relationship to the degree of stress surely might be expected. It is known that intense stress can produce myocardial necrosis from the secretion of catecholamines. Lesser degrees of such secretion in exercise seem to be at least harmless. Indeed, many are paying good money to health clubs on the premise that they are beneficial. If there is a dose-effect for stress, where is the evidence for it in the context of the Buljevac study? MS patients are not protected from the major life stresses that plague their fellows. However, my own experience with a generation of patients experiencing overwhelming major life stresses has led me to marvel at how infrequently MS is activated under such circumstances.

An acceptance of the results of the Buljevac paper would carry with it some implications for which we may not be ready. Would every exacerbation then have a blameworthy event, real or imagined? Would MS patients blame themselves for their self-induced stress and others for the rest? Would their partners and families blame them for ‘fighting (or not fighting) the disease’ or be terrorised by the fear of causing an attack? Would patients take advantage and strain the family unit? Would the court systems be clogged with MS patients seeking redress for their exacerbations, on the basis of subjectively experienced stress? Would courts be deluged, as they were when the link between trauma and cancer was transiently accepted in the US several decades ago? Perhaps the only certainty would be the adequate supply of all-too-willing expert witnesses showing every indication they are not listened to at home.

The case is not proven and there should have been more of the ‘usual suspects’ in the line-up. Some quantification of stress would have been helpful, provided this could be validated at some point. Recall bias is sufficiently treacherous that it has to be undetectable in questionnaire studies, even if they are ever so slightly retrospective.

Having said all of the above, the investigators have executed a difficult prospective study and raised important questions. But there are methodological hedges to trim and longer-term outcomes to consider. Even if the connection can be proven, the lack of relationship between later relapses of MS and long-term outcome could still mean that relapses are more often a misdemeanour than a crime.

REFERENCES
Maybe stress isn’t increasing. Maybe all of what we perceive as stress isn’t bad.