prolong the lives of those suffering, thereby providing the necessity for self-action by the patient.

Perhaps when we advise patients and families who face difficult decisions, we would be better to heed the available evidence about who will do well and who will do badly rather than withholding recommendations because unduly cautious statisticians choose to neglect the downside effects of their theoretical arguments. Neurologists are in an especially favourable position to understand the misery that accompanies chronic, overwhelming brain damage. This knowledge places them in a position to understand the humane needs in such cases and advise families accordingly.

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1 Bates D. Defining prognosis in medical coma. *J Neurol, Neurosurg Psychiatry* 1991;54: 569–71.
2 Levy DE, Bates D, Caronna JJ, *et al.* Prognosis in non-traumatic coma. *Ann Int Med* 1981;94:293–301.

Bates replies:

I am grateful to Professor Plum for emphasising the important exclusions in the International Study on Prognosis in Non-traumatic Coma and appreciate his comments relating to the use of unfavourable early signs. I did not intend to suggest that clinical or laboratory indicators of poor outcome were not to be used as part of the process to make decisions in patient management, and am very conscious of what Professor Plum refers to as the "downside statistical feature" of prolonging an insentient life and the consequent burden on the family. My purpose was rather to emphasise that predictors of poor outcome should not be used as the sole factor in making decisions about life support, though they should be used in discussions with relatives of the patient and with our colleagues in helping to arrive at an appropriate clinical decision.

A prospective study of physical trauma and multiple sclerosis

I read with great interest the article by Sibley *et al.*[1] Because of my own involvement in this particular problem, I wish to make the following comments.

There can be no more difficult task than to conduct epidemiological surveys of multiple sclerosis (MS) because of its unpredictability and symptomatic variability. It is therefore unsuitable for measurements with the yardsticks currently at hand. Indeed, to design an epidemiologically valid study, it would be necessary to match MS patients (not just healthy controls) for age, sex, ethnic origin, duration and geographic sites of residence, living and socio-economic environment, duration and severity of disease, type of clinical course, stage of activity, and number and location of lesions using modern imaging techniques such as MRI. It would be necessary to consider not only patients who have already been diagnosed as having MS, but also those who have been symptomatic but not yet recognised as well as all those patients whose symptoms of underlying MS will not appear until they are subjected to trauma. Most of these problems are not taken into consideration in Sibley's article.

It is germane to point out that the "scientific" evidence of epidemiology and biostatistics overlooks the fact that such studies can at best only be estimates within a cohort and cannot be generalised; epidemiological studies are most useful in providing aetiological clues but cannot be used to deny possible causal relationships.[2] As was pointed out by Schoenberg, "Statistical significance (or lack thereof) does not equal biological significance".

It is difficult to understand, on the basis of what is already known about the pathogenesis of MS, how trauma such as laceration of the hand, contusion of the right finger, a root canal procedure, or a thorn in the foot can possibly lead to the appearance or recurrence of symptoms of MS. Sibley *et al* dismiss the alteration of the blood-brain barrier in the genesis of the MS lesion; in doing so they disregard the numerous recent publications which have amply confirmed this fact, including statements by such authorities as McDonald and Barnes[3] who commented that "A consistent, very early event is a breakdown of the blood-brain barrier which is largely repaired over weeks, leading to marked changes in the size of acute lesions" and by Compston[4] who wrote, "Blood-brain barrier damage is necessary early in the development of focal demyelination".

One cannot expect that all, or even most MS patients will have exacerbations following trauma, since it is a common experience for MS patients to have repeated viral infections without changes in the course of their disease.

The relationship between trauma to the head, neck or back that I have supported, is based upon clinical, neuropathological, and experimental evidence which were reviewed in 1986[5] and based on the obligatory step of the alteration of the blood-brain barrier for the formation of the MS lesion. This has now been amply documented.

Additional problems seemed to have plagued this study: for reasons which are not explained, symptoms alone are not recognised as exacerbations. Nevertheless, diplopa, paresthesiae and vertigo, classic symptoms of MS are quite often unaccompanied by objective changes in the neurological examination. It is curious that Sibley *et al* used 48 hours' duration for an exacerbation as opposed to the more generally accepted 24 hours.[6] Finally, it is difficult to draw any conclusions from data given on the basis of mean annual exacerbation rates for the simple reason that exacerbations in MS are never uniformly distributed; periods of complete quiescence lasting several years not uncommonly occur after a series of several exacerbations within a single year.

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1 Sibley WA, Bamford CR, Clark K, Smith MS, Laguna JF. A Prospective study of physical trauma and multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1991;54:584–9.
2 Schoenberg B. *Neurological epidemiology.* New York: Raven Press, 1978;11, 43.
3 McDonald I, Barnes D. Lessons from magnetic resonance imaging in multiple sclerosis. *Trends Neurosci* 1989;12:376–9.
4 Compston A. Immunological aspects of multiple sclerosis. In: Matthews W (ed) *McAlpine's Multiple Sclerosis*, 2nd ed. Edinburgh: Churchill-Livingstone, 1991; 330.
5 Poser C. The pathogenesis of multiple sclerosis: a critical reappraisal. *Acta Neuropathol* 1986;71:1–10.
6 Poser C, Paty D, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis. *Ann Neurol* 1983;13:227–31.

Sibley et al reply:

We age- and sex-matched MS patients with healthy controls solely to establish the degree of accident-proneness of MS patients. It probably needs to be clearly restated that the patients were used as their own controls when they were not "at risk".

Physical trauma had no positive influence on either exacerbation rate or progression of MS in our group of MS patients as a whole, or in various subgroups divided according to sex, age, degree of disability, or duration of disease—all of these data could not be presented in our paper in the interests of brevity. We have not analysed separately based on sites of residence or socioeconomic factors.

I am sure that Dr Poser is aware that we have no way of identifying MS patients whose disease has not yet been recognised. His statement that some of them will not have symptoms until subjected to trauma, makes causative assumptions that our study data do not support.

With regard to his comments concerning the validity of statistical methods, we believe that it is common scientific practice to generalise on the basis of data obtained in representative samples of a group. The calculation of annual exacerbation rates was for the convenience of the reader; the chi-square calculations were done on actual exacerbation numbers during periods at risk and not at risk for trauma, not on the annual rates.

Our study tested the hypothesis, advanced by others, that trauma, including peripheral trauma, could cause exacerbations of MS. We are happy to see that Dr Poser agrees that peripheral trauma, at least, can be dismissed as a cause. He continues to believe, however, that CNS trauma that causes a breach in the blood-brain barrier can cause new lesions in MS. The anecdotal case reports that form the clinical basis for his belief are selected from large numbers of cases where there is no temporal relationship between trauma and exacerbation and cannot be accepted as valid evidence that trauma is a risk factor in MS.

We agree that if trauma were a causative factor that all traumas would not be followed by excacerbations, since many new lesions of MS are symptomatic. However, a study such as ours should have shown a higher proportion of excacerbations when at risk for trauma in 170 patients over a five year period since the frequency of trauma was high.

The Multiple Sclerosis NMR Group at Queen Square has found that in some patients gadolinium leakage may precede other evidence of new lesion formation; they attribute this to inflammation, not to trauma.[1] Certainly barrier breakdown due to the perivenular inflammatory lesions is an early event, but we believe that the cause of this inflammatory response is unknown and our data suggest that trauma is not a factor in new lesion formation.

Our decision to define exacerbations on the basis of objective neurological changes only are in keeping with the Schumacher Committee criteria for definition of a relapse.[2] The 48 hour minimum duration of new symptoms was an arbitrary departure from the Schumacher criteria to help ensure that fluctuations in symptoms due to fatigue and other physiological factors were not counted erroneously as exacerbations.