Letter to the Editor

With some amazement I read the recent article of Wolfson et al. [1] on the comparison of the latent periods of multiple sclerosis (MS) in different populations. In MS only the age at the onset of the disease is known, albeit often with considerable uncertainty. The authors compare two samples of MS patients, from France and from Canada, for which the ages at the onset of the disease are virtually the same. They apply involved statistical techniques in order to arrive at their conclusions, but it is beyond me that the authors do not realize that there is simply not enough information available to warrant any conclusions.

The authors assume that MS is initiated by some unknown factor early in life, probably before the age of 15. After a latent period which can be of considerable length, the disease becomes manifest. If we assume for reasons of simplicity that the age at clinical onset is known exactly, the length of the latent period is given by the difference of the age at clinical onset and the age at the disease initiation. All this is elementary, but as the age at the disease initiation is unknown (actually the whole chain of events leading to the disease is only hypothetical), how can the authors establish a latent period for MS, or even carry out significance tests to compare the latent periods of two samples of patients?

The analysis of Wolfson et al. is based on the approach of De Gruttola and Lagakos [2] for doubly censored data, i.e., data for which the exact times of disease initiation and of clinical onset of the disease are not known, but only intervals of a certain length containing the time of disease initiation (the susceptibility period) and the time of clinical onset of the disease. In the case of MS, however, the susceptibility period is not known, only postulated. Given the ages at the clinical onset of MS, each choice of the susceptibility period generates a distribution of latent periods. Other assumptions of the susceptibility period lead to other estimates of the latent periods.

The authors conclude that the latent periods of MS in France and Canada are not significantly different. If one assumes, as the authors do, that the susceptibility periods in France and Canada are the same (10–15 years of age, for example), their conclusion is trivial, as the ages at the onset of MS are also virtually the same for the two samples of patients. As nothing is known, one might of course also make other assumptions, e.g., that there are differences in susceptibility periods. The authors discuss this possibility to explain differences in age at onset of MS between low- and high-prevalence countries, but I do not see how one can take for certain that the susceptibility periods in France and Canada are the same. Still another possibility which cannot be completely ruled out is that the whole concept of disease initiation, followed by a latent period, is incorrect.

Wolfson et al. do not seem to I aware of these problems, and propose more research along the same lines. In their discussion they claim that - given sufficient data - their approach should allow one to establish the presence or absence of a difference in latent period distributions between countries with low and high prevalence, with possibly an earlier age at onset of MS in these latter countries. With only the data of the times of the clinical onset of the disease available, this amounts to disentangling the time of initiation and the length of the latent period, but once again it is impossible to solve one equation with two unknowns.

References
