fects in immune tolerance either in time to prevent the further cascade of events or with the administration of drugs to check the degenerative process. As stronger and more specific immune modulators are developed and given at the very onset of the disease, better control of the disease will be attained.

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Is Multiple Sclerosis an Autoimmune Disorder?

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THE PATHOGENESIS OF multiple sclerosis (MS) has been debated for decades. At times the arguments have been based on equal parts speculation, fact, and whimsy. (What happened, for example, to the notion that the increased incidence of MS in northern latitudes occurs because people in these colder regions are more likely to be exposed to pet-borne viruses because their animals remain indoors?) As Mark Twain once quipped, "The fascinating thing about science is that one gets such wholesale returns of conjecture out of such a trifling investment of fact." Some speculation is not always bad, of course, because some concept of what is possible is necessary to develop a model that can be objectively studied.

Both sides[1,2] make valid points here, and there may be more common ground between the authors than is at first apparent. Everyone acknowledges that MS can affect neurons as well as the white matter; the debate is whether the neurons are affected late or early in the process. Acute disseminated encephalomyelitis (ADEM) is a monophasic disorder and may or may not be closely related to MS. Experimental allergic encephalomyelitis does not parallel MS exactly, although the same is true of many animal models of human disease that are nonetheless helpful. And all of the authors acknowledge that MS is a complex disorder with multiple clinical patterns that could be initiated through more than one mechanism. Neither side mentions another intriguing idea: that the immune response in MS could result from a chronic viral infection rather than autoimmunity in the usual sense.

While the autoimmune model may not explain every aspect of MS perfectly, it is difficult to ignore the considerable evidence that immunity plays a major role in MS. Several immune-based treatments for MS have been shown to be clinically effective, and it seems unwise to dismiss the significance of these drugs just because they do not slow the progressive form of MS or because they are less effective than we would like. And although experimental allergic encephalomyelitis is not a perfect model for MS, it has led to the development of treatments, such as glatiramer, that are licensed for clinical use based on randomized clinical trials. The use of control subjects in randomized clinical trials makes it unlikely that a placebo effect would be mistaken for a therapeutic drug response.

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The idea that MS is a genetically determined condition with metabolic dysfunction of neuronal elements is intriguing. But where is the evidence? Magnetic resonance spectroscopy may suggest that neuronal dysfunction occurs early in the course of MS, but standard magnetic resonance imaging more often localizes the lesions in the white matter, especially in the early stages of the disease. Some factors cited as evidence of a metabolic effect (eg, temperature sensitivity of symptoms, stress effects, seasonal fluctuation, geographic effects, etc) are nonspecific and might be plausibly attributed to the MS lesions per se with no implications for pathogenesis. Similarly, one could argue that the lesions' anatomic localization could be explained just as easily by differential targeting by antibodies as by a still-unidentified genetic or metabolic defect. Given the importance of histocompatibility groups to T-cell activation, the link between the histocompatibility alleles and MS would seem to support an autoimmune model of MS as much as a genetic mechanism. And if MS is genetically mediated, even via multiple genes, shouldn't there be more familial MS cases than the relatively small number that we now recognize?

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Submissions

We invite you to suggest controversies and 3 names of potential authors to write about either side of the issue. Do not feel that you need to exclude yourself. Please communicate with E. Steve Roach, MD, Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; phone (336) 716-1619; fax (336) 716-9489 (sroach@wfubmc.edu).