regulatory regimens.[24,25] This will be one of the most important debates to get right in contemporary public health.

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What went wrong in the natalizumab trials?

A 42-year-old woman in Colorado had a history of intermittent episodes of neurological dysfunction and was diagnosed with relapsing-remitting multiple sclerosis. She was treated with interferon-1 alfa, but continued to have episodes of neurological dysfunction and was enrolled into a clinical trial of natalizumab, a novel immunomodulatory agent. Unfortunately, she was one of three patients who developed progressive multifocal leucoencephalopathy and she died.[1–3]

According to her case report, her autopsy revealed no evidence of multiple sclerosis. She had no objective evidence of central nervous system inflammation at any time: her spinal tap analysis at the time of diagnosis was normal, and she never had gadolinium-enhancing lesions on any of her multiple brain MRI scans.[1] The clinical history, brain imaging, and autopsy findings were more consistent with migraines and infarcts than with relapsing-remitting multiple sclerosis.

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. Until recently, no reliable measure of CNS inflammation or demyelination existed. Diagnosis was therefore established on clinical criteria alone. Specifically, multiple sclerosis was defined by two unexplained episodes of neurological dysfunction separated in time and by neuroanatomical region, plus the presence of one or more objective neurological deficits on examination.[4,5] These criteria were devised for research rather than clinical purposes, at a time when most multiple sclerosis trials were done at academic centres and, because of their

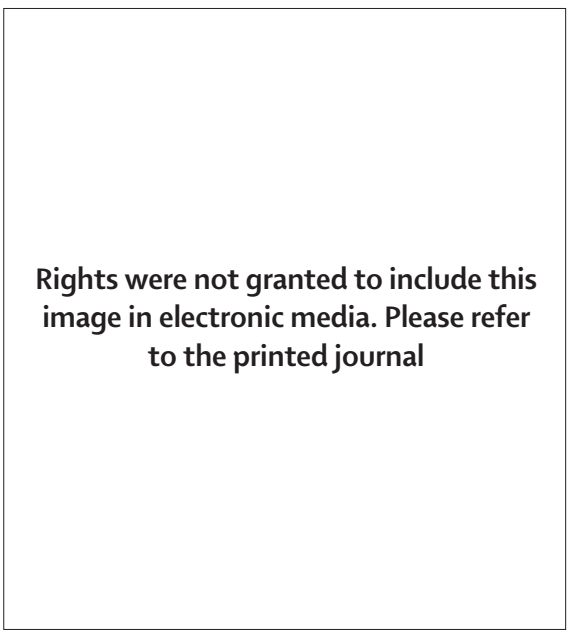
vagueness, require clinical expertise in neurology and multiple sclerosis to use.

Diagnostic criteria for multiple sclerosis have since been revised to reflect developments in technology and an improved understanding of disease pathogenesis. However, the revisions have only served to broaden the definition of multiple sclerosis, rather than improve the specificity of diagnosis. Physicians may now diagnose multiple sclerosis on the basis of either the old clinical criteria or when a single clinical attack is accompanied by objective evidence of CNS inflammation and demyelination on brain MRI and cerebrospinal fluid examination.[6]

The Colorado woman met diagnostic criteria required for the trial of natalizumab on clinical grounds alone, as did 91% of all trial participants.[7] However, clinical trials in relapsing-remitting multiple sclerosis are mostly done in private practice settings and not by specialists in multiple sclerosis, and increasingly by non-neurologists. The accuracy of diagnostic criteria for multiple sclerosis in this setting is unknown, but—if the woman in Colorado is any indication—sensitivity and especially specificity may be poor.

It is vital that entry criteria into clinical trials of relapsing-remitting multiple sclerosis safeguard against the inclusion of patients with misdiagnosed migraine and cerebrovascular disease. The inclusion of such patients calls into question the validity of the results and exposes these patients to risks without any hope for benefit. These problems can be easily corrected by requiring objective evidence of CNS inflammation and demyelination at some point in a patient's disease course before allowing drugs with unknown safety profiles to be tested on them. Even if the Colorado woman had had multiple sclerosis, she had a normal neurological examination at the time of entry into the trial, indicating that she was at low risk for developing disability.[8–10]

When designing entry criteria for clinical trials, we must ask ourselves who are we trying to treat and why? During the past decade, there have been two major changes in the way many clinicians view multiple sclerosis that have contributed to the development of lax entry criteria into clinical trials of relapsing-remitting multiple sclerosis. First, physicians have been led to believe that most patients with this disease will have a poor prognosis, and, second, that drugs work best if given early in the disease course. These shifts clearly benefit the drug companies, because they imply that all patients who might possibly have



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Multiple sclerosis
Coloured MRI scan of plaques (destroyed myelin; pink, arrowed). Healthy nerve tissue is yellow.

relapsing-remitting multiple sclerosis should be treated immediately. However, these views are not supported by what is known about the natural history of the disease. Disability in most patients with relapsing-remitting multiple sclerosis accumulates slowly, if at all, and there is no evidence that aggressive early treatment prevents long-term or even short-term disability. Thus the current sense of urgency to treat is inappropriate.

At the onset of multiple sclerosis, two clinical subtypes can be readily identified: 85% of patients develop a relapsing-remitting course, whereas the other 15% develop progressive disability from the onset, with or without superimposed relapses (so-called primary progressive multiple sclerosis). Patients with primary progressive multiple sclerosis generally have a poor prognosis, and life-expectancy is reduced in this group. However, relapsing-remitting multiple sclerosis is a chronic life-long illness that is rarely fatal. Though one often cited study found that 95% of patients with multiple sclerosis will eventually develop clinically significant physical disability,[11] this figure is a seriously biased estimate of the risk in relapsing-remitting multiple sclerosis. That cross-sectional study was done at a tertiary care clinic and 35% of participants had primary progressive multiple sclerosis. The risk of clinically significant disability reported in most other studies is much lower, ranging

from 35% to 60%.[12–15] In the only prospective population-based cohort study with 25 years of follow-up, only 43% of the cohort progressed to needing a cane or worse.[10] Under the new diagnostic criteria, the fraction of non-disabled patients is likely to increase.[16] Though some have argued that a high proportion of these patients with so-called benign relapsing-remitting multiple sclerosis will develop clinically significant cognitive impairment, there is no evidence to support this claim.[17] In fact, cognitive and physical disability are highly correlated.[18]

If the safety profile of a drug is unknown, enrolling participants who are likely to have a favourable disease course and are not clearly at risk of developing disability over 2 years (the length of most phase III trials in patients with relapsing-remitting multiple sclerosis) exposes patients to unnecessary risk. There are reliable predictors of prognosis that could be used to help separate those who might benefit from treatment from those for whom the risk of treatment probably outweighs the benefit. The best predictors of early and intermediate disease-course outcomes are incomplete recovery from attacks[9,15,19–21] and accumulation of disability within the first 2–5 years after disease onset.[8–10]

Clinical trials of drugs with unknown safety profiles should aim to exclude patients with normal or near-normal neurological examination and target those patients with relapsing-remitting multiple sclerosis at greater risk of disability, such as those with long duration of disease and a moderately abnormal neurological examination, or short duration of disease and at least a mildly abnormal neurological examination.

Despite these concerns, the US Food and Drug Administration has allowed Biogen Idec and Elan to resume open-label natalizumab monotherapy trials in the same patients who met the lax entry criteria.[22] We applaud the fact that the drug is only being used in the tightly monitored setting of a clinical trial. However, under these conditions, it is likely that other patients with benign or misdiagnosed multiple sclerosis will develop progressive multifocal leucoencephalopathy.

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We thank Michael K Gould and Kristin Cobb for helpful reviews of the manuscript. AL-G was supported by grant NS43207-04 from the National Institute of Neurologic Disorders and Stroke. ALG has consulted for Genentech, Amgen, and Biogen Idec, and has been on a speaker's bureau for Biogen Idec. LS has received support from the National Institutes of Health, the National MS Society, and the Phil N Allen Trust, and is a founder of Bayhill Therapeutics and Neurocrine Biosciences.

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