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THE AUTHORS REPLY: With regard to Eisner's comments: we conducted an observational study and used propensity-score methods¹ to create evenly matched cohorts of patients. The propensity-score models controlled for an extensive list of potential confounders, but they were limited to variables that could be obtained from administrative data. Although our results could be biased by unmeasured confounders, the magnitude of the differences we observed makes it unlikely that an unmeasured confounder could have al-

tered our results in favor of open repair. Furthermore, we agree with Eisner that unmeasured confounding is more likely to have led to bias against endovascular repair. Thus, in contrast to the example of the pulmonary-artery catheter, the fact that we found an important difference despite the potential for unmeasured confounders further underscores the importance of our results for clinical practice.

Marc L. Schermerhorn, M.D.

Beth Israel Deaconess Medical Center
Boston, MA 02215
mrscherm@bidmc.harvard.edu

A. James O'Malley, Ph.D.

Bruce E. Landon, M.D., M.B.A.

Harvard Medical School
Boston, MA 02115

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Rituximab in Relapsing–Remitting Multiple Sclerosis

TO THE EDITOR: Hauser et al. (Feb. 14 issue)¹ report positive results of a phase 2 trial of rituximab in relapsing–remitting multiple sclerosis. I wish to draw attention to the Food and Drug Administration (FDA) public health advisory concerning rituximab.² This advisory was recently updated after the reported deaths from progressive multifocal leukoencephalopathy of two patients who were treated with rituximab for systemic lupus erythematosus. Keeping pace with the use of more potent and specific immunosuppressant agents, the incidence of opportunistic infections such as progressive multifocal leukoencephalopathy seems to be increasing. In clinical trials of natalizumab for the treatment of Crohn's disease and multiple sclerosis, progressive multifocal leukoencephalopathy developed in three patients, two of whom died.³ Natalizumab was withdrawn from the market, and after a large postexposure evaluation, it was allowed back on the market with extensive safety instructions. Hence, despite the promising results of the newer generation of immunosuppressive drugs, their safety profiles raise concern. In order to optimize the balance between the risks and benefits of treatment, future trials should both incorporate rigorous safety monitoring and target those patients who have a great risk of disability.

Hans M. Schrijver, M.D.

Westfries Gasthuis
1620 AR Hoorn, the Netherlands
h.schrijver@westfriesgasthuis.nl

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TO THE EDITOR: The use of rituximab, an anti-CD20 antibody, in the treatment of autoimmune diseases, including multiple sclerosis, is surely promising. In their article, Hauser et al. report that CD19 and CD20 have similar expression profiles, and therefore they monitored CD19 cells in the patients with multiple sclerosis who were treated with rituximab. CD19 and CD20 expression is not the same in different stages of B-cell development and function.¹ CD20– autoreactive B-cell clones could, in some cases, mediate the damage in autoimmune diseases.² Therefore, the monitoring of CD19-expressing and CD20-expressing cells could perhaps improve our understanding of the efficacy of rituximab in patients with

autoimmune diseases. Analysis of CD20 expression in peripheral blood could also allow us to establish the relationship between the presence of CD20+ B cells and the immune-mediated damage as shown, for instance, in idiopathic autoimmune hemolytic anemia.³ Finally, this approach may contribute to a better selection of patients who are likely to have a good response to treatment with rituximab.

Raffaele De Palma, M.D., Ph.D.

Second University of Naples
80131 Naples, Italy
raffaele.depalma@unina2.it

Adelina Sementa, M.D.

Moscato Hospital
83100 Avellino, Italy

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TO THE EDITOR: The monoclonal antibody described in the article by Hauser et al. is another addition to the growing list of immunotherapies that improve magnetic resonance imaging (MRI) findings and relapse rates in multiple sclerosis. Previous studies have shown that the use of anti-lymphocytic globulin and total lymphoid irradiation in multiple sclerosis is futile.¹ In multiple sclerosis, acute demyelination can evolve without B cells,² and one third of lesions have no lymphocytes.¹ There is no disease-specific antibody in multiple sclerosis, unlike other autoimmune diseases in which rituximab is effective.

Previous lessons from trials of multiple sclerosis suggest that there is a huge gap between the treatment effect, as assessed by changes on MRI and relapse rates, and the long-term outcome, as assessed by disability measures such as the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite Scale. The gap is bridged, as in this trial, by statistical extrapolation rather than by longitudinal follow-up data. Inflammatory changes in multiple sclerosis (e.g., enhancing lesions on contrast-enhanced MRI and relapses) are probably tissue reactions to neurodegeneration rather than autoimmune in nature. The timeline of MRI changes in the rituximab trial suggests that the effect was probably anti-inflammatory and not due to B-cell depletion.

Unless neurodegeneration in multiple sclerosis is arrested, no form of immunotherapy, however well directed, will contain the long-term progression of disability.

Abhijit Chaudhuri, D.M., Ph.D.

Queen's Hospital
Romford RM7 0AG, United Kingdom
chaudhuri@gmail.com

Peter O. Behan, D.Sc., M.D.

University of Glasgow
Glasgow G12 8QQ, United Kingdom

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THE AUTHORS REPLY: Schrijver raises an important cautionary point. Rituximab has been in use since 1997 for the treatment of B-cell lymphoma and since 2006 for rheumatoid arthritis. Three cases of progressive multifocal leukoencephalopathy have been reported in patients with autoimmune diseases (two with systemic lupus erythematosus and one with vasculitis) who were treated with multiple immunosuppressive agents, including rituximab. The preliminary studies of rituximab reported to date, including the phase 2 study and the recently published phase 1 trial,¹ were not designed to assess long-term safety or to detect uncommon adverse events. Rituximab is not currently approved by the FDA for use in multiple sclerosis.

The expression profiles of CD19 and CD20 are similar, although they are not identical. Both markers are expressed on all mature circulating B cells; however, the CD19 antigen is expressed somewhat earlier in the B-cell lineage pathway (e.g., on pro-B cells). For this reason, CD19 is a reliable surrogate for the presence of residual B cells after treatment with an anti-CD20 antibody. The near-absence of CD19+ cells observed after treatment clearly indicates that the B-cell pool was effectively depleted from the circulation.

The comments by Chaudhuri and Behan highlight the gaps that exist in our current understanding of the pathogenic cascade leading to chronic multiple sclerosis. The relationship among focal inflammation, clinical relapses, and late progression is certainly one of the most important unresolved questions in the field. The ongoing trial of rituximab in primary progressive multiple sclerosis may shed some light on this question. It is often through bedside experiments

— such as the trials of rituximab in multiple sclerosis — that our fundamental concepts of disease causation receive real-life tests.

Stephen L. Hauser, M.D.

Emmanuelle Waubant, M.D., Ph.D.

University of California at San Francisco
San Francisco, CA 94143
hausers@neurology.ucsf.edu

Amit Bar-Or, M.D.

Montreal Neurological Institute
Montreal, QC H3A 2B4, Canada

for the HERMES Trial Group

1. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol* 2008;63:395-400.

Lumbar Spinal Stenosis

TO THE EDITOR: As Katz and Harris (Feb. 21 issue)¹ note, electromyography is not routinely necessary in the diagnostic workup of spinal stenosis. However, a complete electrodiagnostic examination (i.e., nerve-conduction studies and electromyography) can often be quite helpful in differentiating symptoms related to spinal stenosis from those due to a peripheral neuropathy. In general, a patient with clinically significant spinal stenosis will have electromyographic evidence of multilevel lumbosacral radiculopathies with essentially normal nerve-conduction studies, whereas a patient with clinically significant peripheral neuropathy will have just the opposite findings (i.e., abnormal nerve-conduction studies and normal electromyography).² Even when both disorders are present, it is frequently possible to identify the one that is more symptomatic, since electrodiagnostic testing can also delineate the severity of each process.

Patrick Kortebein, M.D.

Central Arkansas Veterans Healthcare System
North Little Rock, AR 72214

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TO THE EDITOR: Katz and Harris did not discuss recent evidence that provides support for the role of physical therapy in the treatment of lumbar spinal stenosis. A randomized trial in 2006 showed that patients who walked on a treadmill with body-weight support and received manual physical therapy improved significantly ($P=0.002$) in measures of disability, satisfaction, and treadmill walking as compared with those who participated in just the treadmill and exercise program.¹ These results were maintained at 1 year. When

evaluating the effects of nonsurgical care, it is important to differentiate what may be standard practice from what is current best evidence-based practice.

Daniel Rhon, D.P.T.

Baylor University
San Antonio, TX 78234
daniel.rhon@amedd.army.mil

1. Whitman JM, Flynn TW, Childs JD, et al. A comparison between two physical therapy treatment programs for patients with lumbar spinal stenosis: a randomized clinical trial. *Spine* 2006;31:2541-9.

TO THE EDITOR: Katz and Harris refer to a study in which “the finding of a wide-based gait among patients with back pain had a specificity exceeding 90% for lumbar spinal stenosis.” In the preceding sentence, this feature is attributed to involvement of the posterior columns. I take issue with both the observation and the interpretation. The study in question, of which Katz was the first author,¹ provided no definition of “wide-based gait,” and the diagnostic value of the sign was not tested in a different population. The reference to the posterior columns is misleading, since normally the lumbar spinal canal contains only the roots of the cauda equina, not the spinal cord with its columns. The cord ends at the level of the first lumbar vertebra.

Jan van Gijn, M.D.

University Medical Center
3584 CX Utrecht, the Netherlands
j.vangijn@umcutrecht.nl

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THE AUTHORS REPLY: We agree with Kortebein that electromyography and nerve-conduction studies are useful in distinguishing the polyradiculop-