increased that the treatment groups will be imbalanced with respect to important patient characteristics in at least one subgroup. Stratification of the randomization is one approach for ensuring balance with respect to certain factors, but the number of factors that can be controlled in this way is limited. Adjustment for patient characteristics in the analysis of the data is another, and such adjustment can therefore be useful in subgroup analyses. Finally, even when the treatment groups are balanced with respect to all important characteristics in every subgroup, false positive interactions between treatment group and a patient characteristic will still lead to biased (e.g., exaggerated) estimates of treatment differences within the corresponding subgroups, reinforcing the importance of properly controlling for type I errors in multiple-subgroup analyses.

Stephen W. Lagakos, Ph.D.
Harvard School of Public Health
Boston, MA 02115

Optic Neuritis

TO THE EDITOR: In her article on optic neuritis, Balcer (March 23 issue)[1] points out that the patient with optic neuritis and multiple white-matter lesions, as seen on magnetic resonance imaging of the brain, is at increased risk for multiple sclerosis (which is correct) and that the treatment of such patients with interferon beta reduces or delays the "development of multiple sclerosis" (which is not correct). No treatment has been shown to reduce or prevent the development of multiple sclerosis, except with reference to a restricted window of time, which is clinically not a very meaningful way to think of therapy for a chronic, relapsing disease. As for delay, surely the optic neuritis must be regarded as the onset of the disease in these patients, so there can be no delay. By reducing the frequency of relapses,[2-4] interferon beta delays the diagnosis of multiple sclerosis — a far less important outcome.

Les Dorfman, M.D.
Stanford University School of Medicine
Stanford, CA 94305

Dr. Dorfman reports having received honoraria from Berlex, Biogen, Serono, and Teva.

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DR. BALCER REPLIES: I agree with Dr. Dorfman that although interferon therapies may not ultimately prevent multiple sclerosis in the setting of acute optic neuritis, a delay in the development of clinical demyelinating events and the diagnosis of multiple sclerosis is not likely to be an unimportant end point for a given patient.

Laura J. Balcer, M.D., M.S.C.E.
University of Pennsylvania School of Medicine
Philadelphia, PA 19104
lbalcer@mail.med.upenn.edu

More on Donor-Derived T-Cell Leukemia after Bone Marrow Transplantation

TO THE EDITOR: In the case reported by Tamaki and Matsuoka (April 20 issue),[1] there is no definite evidence of human T-cell lymphotropic virus type I (HTLV-I) infection in the hematopoietic stem-cell donor, and there seems to be no clonality marker such as monoclonal proviral integration in the donor. We therefore cannot conclude that adult T-cell leukemia–lymphoma (ATL) in the re-

cipient was instigated by undetected HTLV-I in the asymptomatic donor. The possibility of an acquired infection of donor T cells by HTLV-I in the recipient has not been excluded. We propose that the profound immunosuppression attributable to pretransplantation conditioning and prophylaxis against post-transplantation graft-versus-host disease could have accelerated the development of ATL.[2] Even if the donor was a healthy carrier of HTLV-I, proviral integration occurs in only about 0.1 to 1.0 percent of peripheral-blood mononuclear cells. However, although it is "T-cell lymphotropic," HTLV-I can infect extrahematopoietic cell types in vitro.[3-5] Viral-genome sequencing could have shown the source of the HTLV-I.

Daniele Focosi, M.D.
Mario Petrini, M.D.
Ospedale Santa Chiara
56100 Pisa, Italy
focosi@icgeb.org

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THE AUTHORS REPLY: We believe that the brothers described in our report were infected with the same strain of HTLV-I because mother-to-child transmission through breast-feeding is a primary route of infection.[1] Furthermore, HTLV-I has little variation in sequence.[2] Indeed, we detected no difference in 5′–long-terminal-repeat and *env* sequences of HTLV-I provirus between the peripheral-blood leukocytes from the brothers and donor-derived ATL cells. Sequencing the HTLV-I genome is a useless way to determine the origin of the donor ATL clone.

This clone was undetectable in the donor with the use of tumor-specific polymerase chain reaction (PCR), but it was detectable in the recipient three weeks after transplantation. This period was too short for HTLV-I–infected cells to expand clonally after HTLV-I infection in the recipient. In addition, the DNA methylation pattern of HTLV-I provirus in donor-derived ATL cells was similar to that in asymptomatic carriers. These findings suggest that the clone existed in the donor as a minor population below the sensitivity of PCR, although we cannot completely exclude the possibility of a new infection in the recipient after transplantation.

Hiroya Tamaki, M.D., Ph.D.
Osaka Minami Medical Center
Osaka 586-8521, Japan
tamaki@ommc-hp.jp

Masao Matsuoka, M.D., Ph.D.
Kyoto University Institute for Virus Research
Kyoto 606-8507, Japan

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EGFR Mutations in Small-Cell Lung Cancers in Patients Who Have Never Smoked

TO THE EDITOR: Mutations in the epidermal growth factor receptor gene (*EGFR*) occur in 10 to 20 percent of non–small-cell lung cancers, specifically adenocarcinomas, and are associated with the response to EGFR tyrosine kinase inhibitors (erlotinib and gefitinib).[1] However, the results of screening of small-cell lung cancers for *EGFR* mutations have been negative.[2] Thus, small-cell lung cancers are not routinely tested for *EGFR* mutations, nor have they been systematically evaluated for responsiveness to EGFR tyrosine kinase inhibitors.

A 45-year-old woman who had never smoked and who had masses in the right lung, pleura,