Editors' Note: In WriteClick this week, Dr. Sethi comments on the benefits of neurology training experiences in low- and middle-income countries, citing the breadth of pathology and the gratification from being truly needed. Author Mateen remarks on the increasing globalization of the international medical workforce. Dr. Brenner and authors Ristori et al. discuss the molecular immunology of the Bacille Calmette-Guérin vaccination and its effects on Notch signaling.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

INTERNATIONAL ELECTIVES IN NEUROLOGY TRAINING: A SURVEY OF US AND CANADIAN PROGRAM DIRECTORS

Nitin K. Sethi, New York: I read the article by Lyons et al.¹ and the accompanying editorial by Jozefowicz and Birbeck² with interest. It would have been interesting to know if the surveyed program directors had any international neurology training in low- and middle-income countries (LMIC). I am a foreign medical school graduate and completed residency in internal medicine in India before coming to the United States to pursue my neurology residency. During my residency, I saw infectious, tropical, and chronic neurology cases in one large hospital. The experience of training in a LMIC country is very enriching. The workload is so overwhelming that everyone is needed. The friendships that were fostered also ensured future interinstitutional collaborations. Similar to the United States, the standards of formal residency education vary among different residency programs and institutions in LMIC. It would benefit program directors to identify programs and institutions in LMIC where their residents would get a deeply fulfilling learning experience. It will be money well spent.

Author Response: Farrah Mateen, Boston: We thank Dr. Sethi for his comments. We did not survey program directors on their own experiences or backgrounds¹ as the goal was to keep the survey brief and maximize the response rate. It is likely that some program directors attained their degrees or postgraduate training in LMIC. Other program directors may have

traveled abroad for a single experience in LMIC, and it is probable that many program directors have had limited international experience. It is uncertain how program directors' experiences may influence residents' perceptions. It is not necessary to travel abroad to appreciate the value of responsible medical work in welcoming, resource-limited, international settings.

In 2007, a report of radiologists³ found that the number of program directors with Indian birth or background increased from ~1% in 1993 to 3.5% in 2003. In 2008, there were 2,420 medical schools, including just 173 in North America compared to 513 in Latin America and the Caribbean, 446 in Europe, 300 in India, 206 in North Africa/Middle East, and 188 in China.⁴ The global migration of health care professionals, either temporarily or permanently, continues to change the medical education landscape. Understanding these trends, and appreciating that North America is both a recipient of and donor to the international medical workforce, is key for the care of people with neurologic disorders.

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EFFECTS OF BACILLE CALMETTE-GUÉRIN AFTER THE FIRST DEMYELINATING EVENT IN THE CNS

Steven R. Brenner, St. Louis: I read the article on Bacille Calmette-Guérin (BCG) reducing the likelihood of developing multiple sclerosis (MS) after an event of clinically isolated syndrome.¹ BCG upregulates Notch-1 signaling through a nitric oxide-mediated pathway in macrophages.² Notch signaling appears to be involved in the pathogenesis of MS; Notch

receptors are abundantly expressed in inflammatory and demyelinating lesions as well as in experimental autoimmune encephalomyelitis (EAE).³ Modulation of Notch signaling in EAE reduces the severity of immune responses.³ Recombination signal binding protein for immunoglobulin kappa J region (RBPJ), a protein of the Notch signaling pathway that also is involved in Epstein-Barr virus (EBV) infection, is a CSF-related autoantigen in an MS subset.⁴ Notch1C (Notch 1 intracellular domain) transactivates gene expression by CBF-1/RBPJ tethering to DNA. Transactivation of Notch1C is due in part to eliminating CBF-1/RBPJ-mediated repression. The same mechanism utilized by Epstein-Barr nuclear antigen 2 (EBNA2), through molecular mimicry, causes virus-driven immortalization of cells.⁵ BCG vaccination causing upregulation of cellular Notch-1 signaling may restore normal cellular Notch-1 mechanisms and prevent EBV from causing macrophage immortalization with development of the autoimmunity characteristic of MS.

Author Response: Giovanni Ristori, Silvia Romano, Giulia Coarelli, Maria Chiara Buscarinu, Marco Salvetti, Rome: We thank Dr. Brenner for his comments. Prevention of autoimmunity by adjuvant immunotherapy partially depends on inducible nitric oxide synthase,⁶ and the relationship between Notch signaling and Epstein-Barr virus (EBV) would be interesting to determine the mechanisms underlying the converging seroepidemiologic evidences that link EBV to MS.⁷ This relationship is based on the molecular interaction between EBNA2 and RBPJ: EBNA2 functions as a transcriptional activator by interacting with DNA-binding RBPJ, and relieving the transcriptional repression that is mediated by a large multi-protein complex.⁸ The *EBNA2* gene is the most polymorphic of all EBV genes⁹ and is densely targeted by host and virus micro-RNAs.¹⁰ This interaction

may be vital and MS studies on *EBNA2* variants are ongoing. The possibility that adjuvant immunotherapy may counteract the pathogenic loop due to EBV or its genomic variants deserves further research. Moreover, future trials with BCG vaccine in demyelinating diseases might include analysis of EBV status (serology, viral load, genotyping) and Notch signaling components.

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