Editor's Note: A recent case report in the *Ears, Nose and Throat Journal* describes a patient with unilateral epistaxis caused by a blood-sucking leech. While I do not always follow the ENT or parasitology literature, I was inspired to do so by this week's WriteClick post, which features the intersection between neurology and endocrinology, cardiology, and nutrition. The current paradigm of medical education often means that the acquisition of new knowledge outside of our own specialties ends with the third year of medical school. But this increasing compartmentalization of medicine is convenient, not physiologic. Examples of crossover therapies, such as thrombomodulin discussed below, abound. Botulinum toxin migrated from ophthalmology. Amantadine was first developed as a prophylaxis against Asian influenza. Topiramate is now used routinely in weight loss clinics. Each of us needs to find a way to keep in touch with all of medicine—not just our own bit.

Megan Alcauskas, MD

ASSOCIATION OF ALZHEIMER DISEASE PATHOLOGY WITH ABNORMAL LIPID METABOLISM: THE HISAYAMA STUDY

Gerson T. Lesser, Bronx, NY: Matsuzaki et al.¹ noted associations of total serum cholesterol (TC) and low-density lipoprotein (LDL) with frequency of neuritic plaques (NP) but not with neurofibrillary tangles (NFT). In a WriteClick submission, Mascitelli et al.² note that these results are “inconsistent with other studies.” Relatively few lipid-Alzheimer disease (AD) investigations are similarly neuropathologically based. Among these, Matsuzaki et al. and Mascitelli et al. may not be aware of the publications of Kuo et al.³ and of our group.^{4,5} Both of our findings supported the Hisayama findings¹ and presented evidence contrary to the comments of Mascitelli et al.² In 2001, we found that nursing home residents with AD pathology (Consortium to Establish a Registry for Alzheimer's Disease [CERAD]) had significantly higher TC and LDL than residents with dementia with other-than-AD pathology. This was later confirmed in a larger nursing home cohort,

additionally showing that increasing certainty of AD (CERAD-based)⁴ and increasing counts of NP⁵ were each significantly associated with higher levels of TC and LDL. We further confirmed the finding of Matsuzaki et al.¹ of no significant lipid–NFT correlations.⁵ Our data also conflict with the suggestion by Mascitelli et al.² that the results of Matsuzaki et al. might be confounded by statin use; only 6% of our subjects had used statins and, when adjusted for statin use, the lipid–NP relationships were unchanged.⁵

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THROMBOMODULIN AND THE BRAIN: PAST, PRESENT, AND FUTURE

Daniel A. Lawrence, Enming J. Su, Ann Arbor, MI; Karl-Uwe Petersen, Aachen, Germany: The recent Editorial by Dr. Fisher¹ discussed the findings of Giwa et al.² and emphasized that, currently, the anticoagulant thrombomodulin (TM) “is not commonly discussed within neurologic circles,” but that it may have significant advantages over other anticoagulants in the setting of ischemic stroke. We could not agree more with Dr. Fisher's assessment and would like to point out 2 recent studies demonstrating the efficacy and safety of recombinant soluble TM in 2 independent animal models of ischemic stroke.^{3,4} These studies were performed by different laboratories and carried out in different species, with 2 very different model paradigms. Su et al.³ (see also

commentary³) used a photothrombotic model in mice to demonstrate that soluble TM administered after stable thrombotic occlusion of the middle cerebral artery restored blood flow and reduced infarct volume without increasing hemorrhage. In another study, Ryang et al.⁴ confirmed the efficacy and safety of soluble TM in a transient middle cerebral artery occlusion model in rats. We believe that these observations together with those discussed by Fisher should—as indicated by Fisher—“awaken interest in TM by stroke neurologists” and “may help generate attention for a clinical trial of this compound in acute ischemic stroke.”

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NUTRIENT BIOMARKER PATTERNS, COGNITIVE FUNCTION, AND MRI MEASURES OF BRAIN AGING

Cedric Annweiler, Angers, France; Manuel Montero-Odasso, Robert Bartha, London, Canada; Olivier Beauchet, Angers, France: Recently, Bowman et al.¹ reported that a plasma nutrient pattern rich in vitamin D was associated with better cognition and larger brain volume on MRI in older community dwellers. Despite comprehensively estimating nutrients, such studies could be enhanced by measuring regional volumes rather than whole-brain volume to identify specific brain areas protected by vitamins. Since structural brain changes manifest long before cognitive symptoms, accurate morphometric approaches are crucial.² Current automated segmentation algorithms can determine the volume of different regions of interest,³ which may help to clarify vitamins' effects. However, restricting the scope of investigations limits the relevance of findings. An alternative is the measurement of lateral ventricle volume, which is an indirect measure of multipoint atrophy because CSF is under pressure and any parenchymal loss results in passive ventricle expansion.⁴ Modern software can segment ventricles in subvol-

umes, providing insight into the volume of adjacent brain structures. For instance, atrophy of medial temporal lobe leads to ventricle temporal horn enlargement, and expansion of ventricle frontal horn reflects frontal lobe shrinkage.⁵ Future studies should describe regional changes in brain, ventricles, or both to better understand the neurobiological basis of cognitive changes associated with diet, and specifically with the remarkable neurosteroid vitamin D.

Author Response: Gene L. Bowman, Lisa Silbert, Hiroko Dodge, Joseph Quinn, Jeffrey Kaye, Portland, OR: We thank Annweiler et al. for their comments. In this first analysis investigating nutrient biomarker profiles in relation to brain health,¹ we started from the generalizable premise that there would be a distinct nutrient combination associated with brain health marked by well-established global volumetric indices. There are data demonstrating that overall brain atrophy is a measure of age-related brain health, risk for disease, or reserve.^{6,7} Essentially all regions of the brain atrophy with healthy aging⁷; total brain volume is a global index of the magnitude of this phenomenon. Similarly, white matter change has been associated with vascular disease and thus this MRI marker (total white matter hyperintensity volume) would suggest nutrient profiles associated with protection from global vascular disease.

We considered it premature to generate a hypothesis related to specific subregions; there is no a priori reason to expect that the left dorsal medial fasciculus Y is associated with vitamin Z. Practically speaking, we had to resist the temptation to parcel the brain into potentially hundreds of subregions to avoid type II errors. We have subsequently evaluated total ventricular volume (another marker of overall atrophy) and the result is consistent with the use of total brain volume as a marker.

Future studies will address more specific regions guided by this preliminary data. We appreciate the value of using ventricular subregions as ready surrogates for more targeted studies such as of the medial temporal lobe.⁸

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