ing,[2] the value of plasma or CSF levels to predict brain levels of this highly lipophilic coenzyme are not clear. Equivalent doses of CoQ from different suppliers may result in widely different blood levels,[2] and we were not able to explore this important aspect of CoQ bioavailability before designing our study. Attempts to improve the bioavailability of CoQ are underway,[4] and further studies of novel preparations with better brain penetration may be worth pursuing in the future. The question of whether dietary or low doses of supplemental vitamins and CoQ that were permitted could have masked changes in oxidative stress responses due to the treatment interventions is potentially interesting, although difficult to test definitively. Comparison groups of patients with Alzheimer disease and healthy control subjects who were not taking any antioxidant supplements at all would be necessary to address this question. The F2-isoprostane assays were run in a single batch; a reference range for F2-isoprostanes in CSF from healthy subjects run by Montine Laboratory during the same period was 15 pg/mL to 40 pg/mL (90% CI).

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Conflict of Interest Disclosures: None reported.

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Evolution and Animal Models

Carlson[1] is not the first to address the role of animal models in basic research pertaining to advances in clinical medicine or the importance of evolutionary biology and comparative research. However, others have disagreed with his conclusions. For example, Crowley[2] pointed out that of 25 000 basic research articles published in the top 6–ranked journals for basic research, only 1 was associated with a clinically useful new drug in 30 years of publication. The institutionalization of the importance of basic research dates back to the Comroe-Dripps report,[3] but recently, Grant et al[4,5] established that the Comroe-Dripps report was so flawed that the conclusions are not defensible.

In contrast to basic research involving animal models, research involving the human brain revealed facts regarding amyloid plaques and tau tangles of Alzheimer disease, α-synuclein of Parkinson disease, the CAG triplet repeats of Huntington disease, and the motor neuron loss of amyotrophic lateral sclerosis.

In the context of complexity science, evolutionary biology explains why interspecies extrapolation is problematic, if not impossible, in terms of response to drugs and disease.[6] Animalia consists of evolved systems that are differently complex. Small differences in the initial condition of a complex system, such as differences in the regulation and expression of genes, modifier genes, and mutations, can result in 2 otherwise very similar systems exhibiting different outcomes to the same perturbation.

Basic research that uses animal models will continue to find new facts about the fundamentals of biology, just as it has in the past. However, to conflate these new facts with advances from human-based research is disingenuous.

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Conflict of Interest Disclosures: None reported.

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In reply

I agree with Hansen and Greek that basic research using animal models is no substitute for human-based research into disease, and I am puzzled at their assertion that I have conflated the two. I did not claim that basic research translates directly into clinical treatments or even address the ways in which clinical applications may derive from basic research. Instead, my concern was with the limited diversity of animal models being used in modern neuroscience research.[1] Precisely because every species is unique, it is dangerous to focus our research efforts on a small number of species chosen solely because of their utility as genetic models. When our general understanding of neuroscience becomes based on such a small sampling of evolutionary diversity, we run the risk of partaking in the exact kind of extrapolation that Hansen and Greek are wise to caution against.

Nevertheless, their response gives me an opportunity to provide my perspective on the relationship between basic and clinical research. I agree that human-based research is essential to better understanding disease; however, I strongly disagree with their suggestion that clinical advances in neu-

rology are not critically dependent on basic neuroscience research using animal models. Transgenic mouse models have been essential in furthering our understanding of Alzheimer disease,[2] Parkinson disease,[3] Huntington disease,[4] and amyotrophic lateral sclerosis.[5] These insights are, in turn, derived from a vast and deep knowledge base established over decades of research using a variety of species. Where would our understanding of the cellular basis for neuronal excitability be were it not for the squid giant axon? For example, deep brain stimulation[6]—a critically important therapy for Parkinson disease and other neurologic disorders—is beholden to Hodgkin and Huxley's insight gained with a decidedly nonhuman model. Thus, it is disingenuous to suggest that clinical advances resulting from human-based research are not dependent on past and ongoing basic research using animal models.

Determining the return of investments in basic research may be a worthy goal, but it is difficult to do so accurately. Seminal papers can shape entire disciplines, and simple bibliometrics do not account for overall impact. The few studies that have attempted to quantify translation rates have used different methods and focused on different medical specialties, leading to widely divergent estimates. Therefore, conclusive and sweeping statements about the percentage of contribution of basic research to clinical advances are unwarranted.

Every species is unique, by definition. This is why potential treatments, no matter how effective in animals, must be tested on humans before being adopted. But this is also why comparative studies are essential to developing broadly applicable principles. Although no 2 species are exactly alike, all biological systems share certain fundamental features. The best way to further expand our general understanding is to use animal models that are best suited to studying a given biological question, and then determine how general the insights are by applying comparative approaches. Better understanding of general mechanisms can then help guide human-based research into specific diseases. Such an approach does not amount to extrapolation but to informed inquiry.

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Conflict of Interest Disclosures: None reported.

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What Is the True Clinicopathologic Spectrum of Neuromyelitis Optica?

We read with interest the article by Mealy at al[1] on the clinicopathologic spectrum of neuromyelitis optica (NMO)/NMO spectrum disorder. We have the following additional comments on the NMO spectrum:

Recurrent Conus Myeloradiculitis as a Presentation of NMO Spectrum Disorder. A 42-year old woman presented with sudden-onset urinary retention that rapidly progressed to a flaccid paraplegia. Results of imaging studies were negative initially; repeat magnetic resonance imaging 5 days from symptom onset revealed conus myeloradiculitis. Results from extensive testing, including spinal angiogram as well as testing for NMO antibodies and visual evoked potentials, were negative. Results from repeat NMO antibody testing 1 year from the initial symptom onset were positive. Few reports have described conus involvement with NMO[2]; root involvement with NMO is even more rarely described. There are no cases in the current series where there is conus involvement or root involvement.

Intractable Generalized Neuropathic Pruritus as a Heralding Symptom of NMO. A 36-year-old woman presented with intractable generalized pruritus for 3 months, after which she developed quadriplegia with bulbar weakness. Cervical spine magnetic resonance imaging showed longitudinally extensive myelopathy from C2 to C5 with no enhancement. Results from tests for visual evoked potentials were normal, while test results for NMO antibodies and anti–Sjögren syndrome antigen A antibodies were positive. Few studies have described generalized pruritus with NMO.[3] It would be interesting to know the prevalence of pruritus in NMO in the current study.

Is Multiple Sclerosis Immunotherapy Beneficial in Some Patients With NMO? Although reports from previous case series have concluded that multiple sclerosis immunotherapy, including interferon and natalizumab, might not be beneficial in NMO, we reported a case where the patient initially diagnosed as having multiple sclerosis remained stable while taking interferons and natalizumab for many years and was eventually diagnosed as having NMO.[4] It is unclear whether there is a subgroup of patients with NMO who might benefit from some of the multiple sclerosis immunomodulators.

In conclusion, we agree with the authors that given the rarity of NMO, having a national registry or even a regional consortium would help answer some of these questions and shed more light on its protean manifestations.

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