ity from the basal ganglia and the role of intrathalamic neuronal circuits is admittedly not well known. Single-cell recording may show several phases of inhibition-excitation or the reverse in response to afferent stimulation in the normal thalamus. This is a feature of many basal ganglia nuclei[7] and does not preclude a global excitatory or inhibitory alteration occurring in pathological states.

Overall, the evidence for increased basal ganglia output activity in the parkinsonian state remains compelling. Clearly, the pathophysiology of the basal ganglia changes that occur in PD have not been completely elucidated, and it is important to remain open to new findings and ideas. However, we do not believe that the findings that Montgomery[1] provided yet warrant abandoning our fundamental concepts.

[1]Department of Neurology, University of Navarro, Pamplona, Spain, and [2]Department of Neurology, Mount Sinai School of Medicine, New York, NY

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What Sort of Change to Believe In: An Alternate Opinion

David J. Fink, MD and Roger L. Albin, MD

In a recent Message from the Editor, "Translational Research for a New Administration: What Sort of Change to Believe In?" Hauser and Johnston propose an ambitious national plan for medical research, including a "Manhattan Project" against medically important diseases described as a "well-funded top down effort directed at the discovery of useful therapies for disease."[1] They suggest that neurodegenerative disorders are particularly suitable targets for a "top-down" research program, and that a concerted effort could shorten the time from innovation to application, capture the public imagination, and serve as a potential engine of economic growth. We respectfully demur.

The historic examples cited in support of this approach include the NASA moon landing program and development of the polio vaccine. The serious potential pitfall that the editorialists recognize, but choose to downplay, is the important difference between applied and discovery science. Prior advances in rocket and computer technology (both developed for other reasons) meant that a successful moon flight could reasonably be anticipated. The discovery of a method to culture virus in vitro (for which Robbins, Weller, and Enders won a Nobel Prize), coupled with existing expertise in creating vaccines, made the successful development of a polio vaccine highly likely. In both cases, successful application required marshaling of substantial resources to achieve the stated objective, but prior discoveries and existing technologies meant there was a good chance of success. Although there have been major advances in understanding of the pathogenesis of neurodegenerative disease, we are skeptical that enough is known to make large-scale public investment in the development of clinical therapies appropriate at this time. Much remains to be discovered regarding fundamental mechanisms of pathogenesis of these diseases, and we have not advanced to the point of possessing well-validated animal models that allow predictive preclinical testing.

Is there a potential downside to promising success by a project management model to fund research with "well-articulated expectations, transparency of work in progress, and clearly defined deliverables"? We suggest that failure to accomplish arbitrary goals is likely to lead to the perception that the biomedical research establishment is, to use a phrase from the editorial, "just another advocacy group at the public till."[1] Because funding for biomedical research over the next several years is unlikely to increase at a rapid rate, funds diverted prematurely from discovery to applied approaches will invariably cut into the funding for creative investigator-initiated discovery science, the approach proved over the past half century to be the best strategy for seminal discoveries, such as deciphering the genetic code, recombinant DNA technology, the unraveling of cholesterol metabolism, to name a few.

Early indications are that the Obama administration will take a more sophisticated view of science than has been the case in recent years. The appointment of a Nobel laureate to head the Department of Energy certainly points to a change in attitude. We suggest that this is a propitious time for the neuroscience research community to argue forcefully for the important role of discovery science and to lobby strongly for adequate funding for that enterprise, rather than for premature expenditures directed at unrealistic goals. This proven approach is more likely to lead to advances that will lay a foundation for the development of effective therapies that future generations may build on.

Department of Neurology, University of Michigan, and Neurology Service and GRECC, VA Ann Arbor Healthcare System, Ann Arbor, MI

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