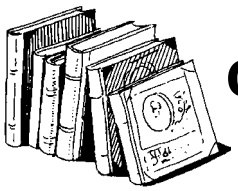

Commentaries

Failing Marks In Optimism

I LIKE TO THINK OF MYSELF AS A PERSON WITH a reasonably accurate perception of the future, neither unrealistically optimistic or pessimistic: expect the worst and hope for the best, probably like most people. I've been accused of being overly optimistic because I plan for the future, assuming that current trends will continue, in contrast to my friend who always assumes and plans for the worst, with excess insurance coverage and multiple contingency plans for disasters most people don't dream about. "You can call me Cassandra, if you want. We can't count on luck."

Which brings me to the current state of clinical neuroscience. A recent lecture by a distinguished researcher in **Alzheimer's disease (AD)** started his talk by noting that five years ago researchers were very optimistic. There were a number of trials planned to test exciting new approaches to treating AD, with vaccines, drugs to reduce pathology and drugs to enhance cognition. The situation looks much worse now, he opined. Progress in treatment has not been made and then popular theories were being abandoned or modified.

My best friend's website for his university physics lab uses the motto, "Experimental physics: where theories come to die." This, of course, extends as well to clinical trials for therapeutics. It sounds like a good thing to reduce amyloid plaque to decrease the pathological burden in AD, and there's undoubtedly an important insight to be learned from a drug that does indeed reduce the amyloid plaque load but which sadly makes the dementia worse, but what that insight yields remains murky. Mitochondria are dysfunctional in Parkinson's disease and drugs that "enhance" their function should help the disease; but, although CoQ10 "works" in animals, it does not in Parkinson's disease.

In a cartoon caption, one scientist turning to another, "What's the opposite of, 'Eureka?"

I think of the study of neurological disorders being akin to fractals: the closer you look, the more complicated they become. Twenty years ago the gene for **Huntington's disease (HD)** was discovered. Not only was this a breakthrough for HD, but it also was the unearthing of an unknown mechanism for genetic diseases, the "excess triplet repeat disorders." This led to the discovery of many other excess-repeat disorders, doublets, triplets, quadruplets, with different constellations of base-pair sequences. But Huntington's disease is no better treated than it was 20 years ago, or maybe 100 years ago. In fact, as with other late-onset neurodegenerative disorders, we still can't even determine when it begins.

Patrick Kennedy has been trying to focus the attention of politicians, the business community and the general public on the public health problems due to brain diseases. He does this partly by discussing not only the devastating effects that these disorders have on the individuals affected, and their families, but also their economic consequences. The economic effects of the dementias are gigantic, and escalating rapidly. He points out the obvious importance of investing now and investing heavily, very heavily, in heading off a problem that will become ever more devastating as our elderly population increases and our younger population decreases. The economics, he argues, are very clear. There is a greater economic reward to be had by *investing* in understanding neurodegenerative disorders, than there is in oil recovery from the oil sands in the Midwest.

Recently, at a major Washington, DC Alzheimer meeting, the Department of Health and Human Services announced a large push to better treat Alzheimer's disease, by funding some new, novel trials. I am skeptical that this is a wise investment. Of course I think it's wiser than building bridges to nowhere, or paying for nuclear weapons, but testing drugs in human trials when we don't have reliable ideas about how the disease starts or advances is a benign waste of money. We need the public to understand that spending money on research is, in fact, an investment, both in human capital and in financial capital. And we need to start by investing primarily in understanding disease processes, and not in splashy studies with a thin rationale.

The Michael J. Fox Foundation is investing heavily in a study that follows newly diagnosed Parkinson's disease patients, measuring as much as possible, in the hope that biomarkers will be found that will help us monitor disease progression in a way that is more accurate than our current approach of eyeballing the patient with a few physical and mental exercises to which we apply numerical scores. This is a no-loss proposition, accruing information that will be useful in clinical trials, unlike the drug trials for slowing disease which either work or don't. But it's not going to solve Parkinson's disease.

The focus should be on causality and to do this requires larger investments in genetics, molecular biology and the development of animal models and if this reduces the amounts invested in clinical trials because of tight budgets and congressional earmarks then we will suffer the consequences, as we are right now.

– Joseph H. Friedman, MD

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Correspondence
e-mail: joseph_friedman@brown.edu