Massachusetts Institute of Technology

THE FUTURE POSTPONED

Why Declining Investment in Basic Research Threatens a U.S. Innovation Deficit

Illustrative Case Studies

A Report by the MIT Committee to Evaluate the Innovation Deficit

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ALZHEIMER'S DISEASE

We Are Seeing Breakthroughs in Treating Cancer—Why Not Alzheimer's?

In the past two years the FDA approved 19 new cancer drugs, and more are in the pipeline—including a powerful new class of immunotherapies that have the potential to transform many deadly cancers into managable chronic conditions. In contrast, during the past decade not a single new drug for Alzheimer's Disease has been approved. Yet over 5 million Americans currently suffer from Alzheimer's—more than for most forms of cancer—and AD prevalence is projected to double in coming decades.

The disparity is shocking, but the reason for it is quite simple: cancer is much better understood than AD. And that in turn stems from more than four decades of sustained investment in basic research into the biology of cancer, beginning in 1971 when President Nixon launched the "War on Cancer." Within a decade, the budget of the National Cancer Institute had tripled. And by the end of the century, enough was known about the mechanisms of cancer and potential targets and pathways for drug therapies that pharma and biotech companies could begin to invest large sums of private capital in drug development with a reasonable chance of success. Today's bounty of oncology drugs is the result, but it would not have happened without the foundational knowledge from which to begin.

Alzheimer's Disease has its own unique challenges. AD drugs will be more costly to develop because of the need to follow patients over longer periods, the expense of current neuroimaging techniques, and the difficulty of brain biopsies. Even more challenging is that the blood/brain barrier blocks most drugs—and all large molecule drugs—from even reaching affected cells. But even before drug development can begin, many basic questions remain unanswered: very little is known about what causes AD, how and when it begins, how it progresses, and whether it can be slowed, arrested, or reversed. The foundational knowledge is simply missing. Yet Medicare spending for Alzheimer's treatment is now $150 billion per year and growing rapidly. Private burdens are high too—last year caregivers provided 17 billion hours of unpaid care for AD family members. Total public and private costs in the U.S. are expected to reach $1.2 trillion by 2050.

There are, however, real opportunities for progress. One might be simply to slow the aging process itself, by altering what appears to be an internal "clock" that drives the process. There are strong but imperfectly understood links between nutrition and human development beginning in utero and continuing throughout life, and it is well established that sharply restricted, low-calorie diets can slow the aging

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clock. If we understood the links better, could drugs or sophisticated nutritional interventions be found that have the same effect? In fact, drugs that activate a particular group of genes known as sirtuins are showing promise in extending lifetimes and mitigating age-related diseases in animal models, but they need further investigation and exploration of their impact on Alzheimer's.

Another opportunity might come from exploring in detail how brain cells communicate with each other—in effect mapping and understanding the brain's neural circuitry and comparing the circuit diagrams of healthy versus AD patients. For some other brain diseases—severe depression, Parkinson's disease—electrical stimulation of the brain has proved helpful. If we understood how the neural circuitry was affected by Alzheimer's, might a similar non-invasive electrical stimulation approach be of use?

Finally, it is becoming clear that there are likely many causes of Alzheimer's—many different genes that increase the risk. Yet virtually all of the clinical trials of potential AD drugs so far have focused only on a couple of genes—those that appear to trigger early onset forms of the disease. Classifying AD patients by their genetic variations, identifying the relevant genes, and understanding the mechanisms that they control or influence might lead both to a deeper understanding of the disease and to potential targets for drug development.

So it is a good thing that the "War on Alzheimer's" is beginning, with the passage of the National Alzheimer's Project Act (NAPA) in January 2011 and the creation of the Brain Initiative in 2013 which coordinates brain disease research efforts at NIH, NSF, and DARPA. Just as with cancer, it will likely take decades of sustained and rising investments in basic research to understand Alzheimer's, other dementias, and the fundamental biology of the brain well enough that drug development has a reasonable chance of success. Yet under current funding constraints, the National Institute of Aging can fund only 6 percent of the research ideas it receives. If we are serious about mitigating the human tragedy of AD and reducing the huge financial burden of caring for millions of affected seniors, then the time to start these investments is now.