

Alzheimer's Disease

Modernizing Concept, Biological Diagnosis and Therapy

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Perspectives on Alzheimer's Disease: Past, Present and Future

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Abstract

Alzheimer's disease, as a chronic brain disorder, is the prototype problem for the *Grand Global Challenge* in healthcare. The key quandary is how to balance the relative 'costs' of investing in research on 'prevention' (to delay disabilities) with the *scale-price* of healthcare services for burgeoning populations with ever-increasing lifespan. The public policy options are limited to: (a) either invest massive funds into research on *prevention* or, (b) develop plans to *ration* healthcare. The scale of the pending health-economic crisis mandates bold scientific initiative(s) to address this grand global healthcare dilemma. Thus the essential global scientific challenge is to resolve the question of: '*How to accelerate the discovery-development of cures for chronic brain diseases – such as dementia/Alzheimer's disease?*' In spite of remarkable recent advances in the neurobiology of neurodegeneration, there is a growing cynicism regarding current paradigms of drug development due to the (a) lack of effective treatments for dementia, (b) bleak prospects for a dramatic breakthrough in therapy development anytime soon, and (c) inadequate conceptual models of neurodegenerative diseases. Notwithstanding these concerns, many believe the prospect of delaying the onset of disabling symptoms within a decade is an attainable goal, *provided we can surmount several scientific, administrative, and financial impediments*. Among these obstacles the limitations of current conceptual models about etiologies of the disease is an important factor. A quantum shift in current approaches to therapy development requires the adoption of alternative paradigms; such as a *systems failure* model of dementia – based on *general systems theory*.

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'The human pain and financial burden of Alzheimer's is so great and the potential breakthroughs in science are so encouraging that a 'Manhattan Project', 'Apollo Project', or 'Human Genome Project' approach to ending Alzheimer's is more than justified. The Alzheimer's Solutions Project is in the best American tradition of solving a big problem with a big vision and a big effort. A public-private partnership is the best collaborative approach to achieve that vision as rapidly as possible. It is the combination of, first, the scale of the crisis and, second, the breadth of the new science which makes this focused, intense investment and project management approach worth implementing.'

Former Speaker Newt Gingrich, Co-chair of the Alzheimer Study Group (ASG), in his testimony to 111th Congress, March 2009.

Quandary of Alzheimer's Disease: Prototype Problem for a Grand Global Challenge

A metaphor for the present-day dilemma facing the global healthcare enterprise was described 3,000 years ago in Greek mythology. The legend of Tithonus depicts a man who cheated death, but whose immortality became a curse rather than a gift. Eos, the goddess of dawn, loved Tithonus so much that she asked Zeus to make him immortal, but she neglected to ask for eternal youth (health) as well. Consequently, Tithonus lived forever but grew extremely old and progressively becoming decrepit and demented.

Modern society is confronting the same quandary as Eos, except on a larger and more complex scale as we confront the economics of healthcare. Now, the *grand global challenge* is to balance the relative '*costs*' of discovering and developing interventions to prevent disability (i.e., the *quest for eternal health*) with the *scale* and *price* of *virtual immortality* (i.e., healthcare for growing populations with an ever-lengthening lifespan).

The public policy options – solutions to this predicament – are limited to two choices: either (1) we invest massive funds to expand research on *prevention* (i.e., disease-modifying interventions to *reduce* the prevalence of costly disabilities), or (2) we start developing plans, the political resolve and the moral fortitude to *ration* healthcare for an aging population.

The Longevity Revolution – Pending Calamity in Healthcare-Economic

Since the Industrial Revolution, improvements in public health, medicine, and nutrition have steadily increased life expectancy. In developed countries, the median age in 1900 was 45 years, today that norm is gradually extending beyond 80 years. This ongoing '*Longevity Revolution*' has dramatically increased the proportion of the population that will survive beyond the 8th, 9th, and 10th decades of life. The '*oldest old*', those over age 80, comprise the fastest growing segment of the population. A significant proportion, perhaps as high as 4 out of 5, of the population born after the WWII era, the so-called 'baby boomers', are destined to live an additional 30–40 years beyond the traditional retirement age of 62–65 years old.

One of the unintended consequences of this longevity revolution is the unprecedented growth in the demand for health-related programs, services, and products. The pending expansion of the 'health market' is due to the nearly exponential increases in the incidence of disabilities after the age of 65 years. These demographic trends – increasing lifespan and the changing patterns in the prevalence of chronic disorders, such as dementia – foretell a major global public health crisis.

The longevity revolution, which already has had a profound impact on society, will require tectonic shifts in thinking about societal priorities. In light of this pending healthcare tsunami, all developed countries need to reevaluate their current social values systems, paradigms, and public policies across vast arenas of society including: the politics of entitlements, economics of pension plans and social security, labor and retirement,

housing and social services, healthcare (including medical insurance, long-term care, and medications) and, most importantly, *investments in research on prevention*.

Simply stated, the scale of the predicament requires new thinking beyond attempts to modify the current systems for financing healthcare and/or delivering services. Traditional constructs to public health will not be sufficient to address the pending healthcare challenges associated with the aging of millions of baby boomers. Unfortunately the core problem of *healthcare in an aging society*, which includes several complex components, does not offer easy or simple solutions for public policies. Thus, a solution might be more readily attained by first focusing on a smaller or more manageable prototype of the larger problem as a preliminary step.

Alzheimer's Disease: A Model for Solving Healthcare Challenges

Among the multitude of contributors to global public health crisis, Alzheimer's disease represents an ideal prototype to serve as a proxy for a number of chronic conditions that require prolonged healthcare and consume costly resources. Neurodegenerative diseases such as Alzheimer's disease and other chronic brain disorders represent a unique class of disabilities not only due to their profound economic impact but also their psychosocial ramifications. The most common clinical features of these unremitting brain conditions – progressive functional impairments of cognition, motor skills, and affect – eventually lead to total dependence on labor-intensive care to sustain life. Due to increasing lifespan, the average period of disability for these chronic conditions is gradually being prolonged. At-risk individuals destined to survive beyond the 9th or 10th decade of life now face the prospects of nearly 30–40 years of disability associated with total dependence for personal care, increasing economic burden and deteriorating quality of life.

The enormous scale of the pending crisis in health-economics mandates a bold vision and a compelling scientific agenda to address this grand global healthcare dilemma. To this end, the most critical public policy issues revolve around the question of '*What needs to be done to accelerate the discovery-development of cures for chronic brain diseases – such as dementia/Alzheimer's disease?*'

In short, the grand global challenge – *problem [P]* – can be conceptualized as the product three variables, namely: (1) *increasing numbers [N]* of individuals at risk for various chronic disabilities, (2) *ever-increasing duration [D]* of disabilities, e.g. 30–40 years and, and (3) the *rising cost [C]* of labor-intensive long-term care. Thus, the most effective long-term solution of the problem [$P = N \times D \times C$] will require formulating public policies and/or initiatives designed to expand global investments in research and development (R&D) programs/initiatives aimed at decreasing the value of [*P*], either by: (1) *prevention* – reducing the number of people with disability or at risk; (2) *more effective interventions* – shortening the duration of disability, or (3) *lowering the cost of care* – new models of care.

Grand Global Challenge – Prevent Alzheimer by 2020

The primary argument of this paper is that the most effective long-term solution to the looming healthcare crisis is to substantially accelerate the discovery and development of therapies for prevention. A broad spectrum of interventions is needed to maintain the independent functioning of older people and delay disabilities for as long as possible. However, huge investments of funds for research by governments or private entities are not likely to materialize without a compelling scientific agenda.

The justification for a huge infusion of public funds into ‘big science’ will require not only a credible scientific rationalization but also a realistic strategic plan for effective utilization of sustained investments in research over long periods of time, e.g. 10 years or more. This 10-year strategic business plan needs to defend the heavy investment of funds into global research and development efforts as well as demonstrate the capabilities for streamlined project management approaches, i.e. the adoption of flexible administrative systems that enable rapid decision-making and can handle unexpected opportunities or breakthroughs. Organizational structures and decision-making processes for supporting research projects within existing government agencies, industry, foundations or academia simply cannot meet the needs of the rapidly-evolving scientific world.

In order to mobilize the scientific community towards the objective of formulating such a 10-year business plan, the *Campaign to Prevent Alzheimer’s Disease by 2020 (PAD2020)* was launched in 2009 [1]. The mission of the Campaign is to develop a comprehensive action plan for the: (a) expansion of global research capabilities, resources, and infrastructure, and (b) discovery and development of a broad spectrum of interventions targeted towards disease modification and/or prevention of neurodegeneration.

The overall goal of the *PAD2020 Campaign* is to reduce the prevalence of Alzheimer’s disease and other brain disorders that affect memory, movement, and mood by 50% within the decade – eventually aiming to prevent the disease entirely. The initiative is based on the premise that a modest delay of 5 years in the onset of disability will reduce the cost and prevalence of the disease by half.

The designation of prevention as target for a global initiative does not imply a promise or a guarantee for disease eradication, but rather, the acceptance of a global goal to mobilize coordinated efforts and a commitment to focus resources towards the achievement of this goal. The enterprise will neither seek nor ask for an assurance of success by the scientific community within the decade; it will merely provide a framework for strategic planning and encourage stretch goals from researchers.

The concept of prevention (defined broadly to include primary, secondary and tertiary prevention) is a clear statement regarding concerted efforts towards a strategic objective to solve the macroeconomic problems of an aging society. The adoption of this goal will not only provide a unifying theme for planning but also offers a conceptual framework for addressing complex relationships among issues concerning science, technology, economics, finance, and public policy.