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

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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

Key Words -

Alzheimer's disease, dementia, neurodegenerative disorders, prevention, treatment, interventions, PAD2020, models, modeling systems, systems failure, general systems theory, public policy, research funding, healthcare, health economics, public health, diagnostic criteria, guidelines for diagnosis, drug discovery, therapy development.

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*.

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 3000 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:

1- Either, we invest massive funds to expand research on ***prevention*** (i.e., disease-odifying interventions to *reduce* the prevalence of costly disabilities);
2- Or, 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 8^{th}, 9^{th}, and 10^{th} 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 health care 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 (AD) 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 AD 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-intense 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 9^{th} or 10^{th} 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×D×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,
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 ten-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 ten-year business plan, the *Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020)* was launched in 2009 [2]. 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 five 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.

A global strategic goal to prevent Alzheimer's disease within a decade will be difficult and costly. However, the challenges for this type of a 'big-science' enterprise are no less daunting than other great human endeavors of the past such as the Transcontinental Railroad (1862-1860), championed by Abraham Lincoln and completed in 7 years; the Panama Canal (1904-1914), championed by Theodore Roosevelt and completed in 10 years; the Manhattan Project (1939-1945), championed by Franklin D. Roosevelt and completed in 6 years; the Apollo Program (1961-1969), championed by John F. Kennedy and completed in 8 years; the Human Genome Project (1990-2000), championed by William J. Clinton and completed in 10 years.

Prevention: A Strategic Goal for Health Care Crisis

During the last three decades, Alzheimer's research has made remarkable progress in understanding the neurobiology of the disease, and the field has attracted some of the best minds in the world to solve the puzzle of this brain disorder. However, in spite of the important advances there is a growing disappointment among all stakeholders with the:

a) Lack of effective treatments for Alzheimer's disease/dementia,
b) Bleak prospects for a dramatic breakthrough in therapy development anytime soon, and
c) Inadequate conceptual models of neurodegenerative diseases.

The public's impatience with the slow pace of progress in developing therapies for dementia is understandable. The burden is now on the scientific community to respond to the growing disillusionment by reversing this lack of progress. Notwithstanding the growing cynicism regarding current paradigms of drug development, a significant

portion of the scientific community believes that the prospect of delaying the onset of symptoms and eventually preventing Alzheimer's disease within a decade is an attainable goal, *provided we can surmount several scientific, administrative, and financial impediments*.

The full spectrum of efforts in therapy development – from discovery to translation of knowledge on the neurobiology of the disease into practical applications - faces an array of barriers. The critical rate limiting factors that influence the pace of therapy development include: inadequate funds, high cost of clinical trials/studies, lack of appropriate models and modeling systems, and antiquated management of discovery and development programs. In order to develop strategies to surmount these numerous hurdles a series of 'Think-Tank' style research planning meeting were organized under the umbrella of Leon Thal Symposia – LTS'07, LTS'08, LTS'09 and LTS'10 [1, 3-6]. Now under the aegis PAD2020 Campaign, these Think-Tank meetings are continuing to seek solutions to the grand global challenge of prevention. PAD2020 Workgroups (WG), have been organized to address essential questions in five generic areas of drug discovery and development for prevention:

- *Science* - What are the scientific and technological obstacles or problems that must be surmounted?
- *Infrastructure/Resources* - What types of infrastructure and resources will be needed by such an undertaking?
- *Regulations/Administrative* - What are the regulatory and/or intellectual property issues that need to be addressed to accelerate therapy development?
- *Organization* - What type of project management team and organizational/administrative structure will be needed outside of governmental bodies?
- *Finance* - What new and different paradigms for financing are needed for such a massive 10-year international initiative?

Exploring New Conceptual Models of Dementia

Current conceptual models of AD, which have enjoyed nearly universal acceptance, have proven to be inadequate in providing effective targets for treating complex brain diseases, such as Alzheimer's syndrome, which essential reflects 'systems failure[s]' in an array of inter-related neural networks. The recent disappointments of Dimebon, Semagacestat, and Flurizan, along with the lackluster preliminary results from other ongoing clinical studies have highlighted the limitations of current conceptual models of the disease, and raised concerns that therapeutic targets currently under investigation may not yield the robust treatment effects (vis-à-vis clinical outcomes) that were anticipated. This uncertainty has begun to recalibrate the thinking in the field about alternative options. Scientists in academia and industry are now ready to reassess many firmly held ideas, assumptions and paradigms of therapy development.

One explanation for the lackluster performance of current drug development paradigms may be the failure of prevailing ideas about the pathogenesis of the disease to fully explain the complex relationship between the clinical and biological phenotypes of the disease. The growing doubts and questions about the ultimate success of hitherto promising therapeutic targets provides a compelling reason for exploring the prospects for different or novel conceptual model[s] of dementia [7].

The enormous scale of the grand global challenge mandates bold, even radical, shifts in thinking about research priorities and paradigms for therapy development. There is an urgent need for new ideas to justify the significant expansion of resources that will be needed to develop a broad spectrum of disease-modifying interventions for prevention and/or the delay of symptom onset.

The PAD2020 virtual *WG on Novel Conceptual Models of Dementia* is an illustrative example of a multi-national collaborative effort to promote new thinking about Alzheimer's disease/dementia and other neurodegenerative disorders. The WG will function as an open forum for integrating diverse perspectives about dementia, including knowledge derived from different disciplines and levels of abstractions ranging from molecules to behavior. The endeavor is not intended to be an exercise in denigrating or promoting any particular theories but rather will focus on combining intellectual resources to yield a novel synthesis. The membership of the WG, which consists of key opinion leaders from academia, industry, government and private foundations, will reflect the critical mix of expertise from all relevant areas of science essential for this model building exercise.

Among the array of scientific obstacles to therapy development, the most crucial factors are the limitations of current conceptual models and ideas about etiologies of the disease. The mission of the WG is to lead a comprehensive assessment of all theories on the pathogenesis of Alzheimer's syndrome and proposed alternative conceptual model[s]. The aim is to facilitate an objective analysis of the utility of current assumptions concerning the critical cascade of biological events during the full clinical course of the disorder.

The final end product of this endeavor will integrate current knowledge about the syndrome in the formulation of one or more alternative conceptual model[s]. The expectation is that this process will identify gaps in knowledge and potential barriers to advancing the discovery and development of disease modifying or preventive therapies. These new models should: a) readily account for both *biological* and *clinical* phenotypes of the syndrome, b) accommodate the full-spectrum of the clinical features of the disorder (ranging from pre-clinical to terminal stages); c) address the issue of mixed pathologies in Alzheimer's syndrome, including how these pathologies interact and contribute to symptom development; and c) generate plans for crucial studies needed to determine the validity of these alternative models.

After three decades of remarkable progress of research on the biology of Alzheimer's disease it is now time to take stock of the advances and chart new directions for exploration. Currently there is growing recognition that the cascade of neurobiological processes associated with the disorder start many years before the appearance of any clinical indicators or objectively measurable impairments of function. Thus, and additional challenge in formulating a new conceptual model of the syndrome is to enable seamless differentiation, in the preclinical stages of the syndrome, of affected people from those who are unaffected but at elevated risk for dementia. The recent exercise in revising the 27-year old diagnostic criteria, *'NIA-AA Workgroups on Diagnostic Guidelines for Alzheimer's disease'* [8-11], has underscored the need for engaging the leaders of the field in a comprehensive evaluation of all prevailing ideas concerning the pathogenesis of Alzheimer's syndrome [2].

'Systems Failure'- A Different Paradigm for Alzheimer's Disease:

One illustrative example for a quantum shift in thinking about Alzheimer's syndrome is the proposal to replace current approaches with a *systems failure* model for explaining the neurobiology of this complex brain disorder. The core premise in a systems approach is to that the syndrome can be conceptualized in terms of progressive failures in an array of interconnected complex systems or neural network(s). The key explanatory concept of this model is that is that the syndrome is not the linear result of a unitary etiologic factor.

The operational framework for such a model does not rely on a single theory. Rather, this embedded-set model approach requires understanding the complex interactions among several predisposing biologic events, including changes that occur in sequence and/or in parallel. The model would explain functional relationships among key components of a system and identify approaches to optimize the functioning of the overall system by examining the character of its constitutive components. The explicit challenge for this conceptual framework is to shift the focus of work towards solving the complex interactions necessary to maintain or restore the functionality or optimal performance of 'the system', which could be defined by functionality of synapses, a neuronal network, a well-defined anatomical structure, or a higher-level emergent characteristic within the system, such as memory.

A conceptual model for neurodegenerative disorders based on *general systems theory* is optimally suited to bring about rapid changes in the current paradigms of therapy development. The formulation and validation of a model for a multi-genic disorder (e.g., Alzheimer's syndrome) based on systems theory will require:

- identifying all key etiologic components
- understanding the sequence interactions of crucial events, and

- developing multiple strategies aimed at preserving/maintaining the functionality of the system

Such a multi-factorial model of the syndrome (or neurodegenerative processes in general) will require drastic changes regarding research philosophies in therapy development. In particular, the discovery of new therapeutic targets intended for prevention will require the adoption of a different way of thinking about the full spectrum of pathogenesis. For example, it is well known that the most proximal pathological events associated with the clinical features of the disease are synaptic failure, dendrite pruning, and loss of neurons; therefore, new therapeutic targets should focus on protecting against synaptic dysfunction or repair and regeneration of affected neurons. These therapies for prevention are more likely to succeed when applied in the early, pre-clinical (or asymptomatic) stages of the disease rather than after symptoms appear. Thus, disease-modifying interventions need to be developed so that they can be delivered decades before the first symptoms appear.

The prime justifications for exploring alternative models of dementia are:

-Presently there are no effective treatments. The lackluster productivity of current drug development paradigms mandates the need to explore different conceptual model(s) of dementia. There is an urgent need to enrich the pipeline for therapy by discovering novel promising therapeutic targets.

-Purely competitive research model of separate groups working by themselves simply will not deliver solutions to this complex problem. A coordinated effort in a non-competitive environment is necessary for validating all of the potential therapeutic targets. Such an open process for sharing information across research groups (in academia and industry) will enable us to: 1) quickly rule in or out particular approaches, 2) avoid redundancy and blind attacks that lead to ambiguous and/or costly clinical trials, and 3) rank targets with the appropriately focused strategy for development.

-The multitudes of neurobiological processes leading to the syndrome appear to start decades before any objectively measurable impairments of function. Thus, a conceptual model of the syndrome is needed that will enable seamless differentiation of affected from unaffected people, as well as asymptomatic people who are at elevated risk for dementia but in the preclinical stages of the syndrome. The goal is to understand the transition from ‘normal’ to pathological.

-Alternative models of Alzheimer’s syndrome pathogenesis are needed to address the issue of mixed pathologies in differential diagnosis, clinical studies, and treatment

Arguably, the mission of the WG is a very ambitious undertaking laden with complex challenges. Yet, at this critical junction, the field cannot afford to be deterred by the countless difficulties in identifying the many facets of the underlying biology of Alzheimer’s disease and related dementias. The search for alternative conceptual models for Alzheimer syndrome will address the specific needs of: a) differential clinical diagnosis, b) discovery and development of novel therapeutic targets, c) discovery and

validation of risk factors, and d) discovery and validation of surrogate markers of disease progression.

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