

Featured Articles

A roadmap for the prevention of dementia II: Leon Thal Symposium 2008

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Abstract

This document proposes an array of recommendations for a *National Plan of Action* to accelerate the discovery and development of *therapies to delay or prevent* the onset of disabling symptoms of Alzheimer's disease. A number of key scientific and public-policy needs identified in this document will be incorporated by the Alzheimer Study Group into a broader National Alzheimer's Strategic Plan, which will be presented to the 111th Congress and the Obama administration in March 2009. The Alzheimer's Strategic Plan is expected to include additional recommendations for governance, family support, healthcare, and delivery of social services.

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1. Introduction

The need to rethink and work toward radical changes in the current paradigms for drug discovery and development of therapy is mandated by the pending healthcare crisis. Several sobering statistics underscore the urgency of the public-health problem. Currently, an estimated 2.4–5.2 million Americans have Alzheimer's disease (AD) [1,2], and this number is expected to increase to as many as 7.7 million people by 2030, and 11–16 million people by 2050 [3]. Caring for people with AD and other memory disorders currently costs about \$100 billion annually, and threatens to bankrupt Medicare and Medicaid. Moreover, the disease has an incalculable financial and emotional impact on families, caregivers, and employers, and this impact will grow

as the disease becomes more frequent. The imperative could not be greater for a massive and comprehensive effort to delay and ultimately prevent dementing illnesses.

The recommendations for action presented here represent the culmination of three think-tank meetings and the collective thoughts of over 70 worldwide leaders in dementia research. The list of contributors to the ideas in this document, as well as the participants of the Leon Thal Symposium on the Prevention of Dementia 2007 (LTS'07), the Webinar on Prevention of Dementia October 2008, and the Leon Thal Symposium on the Prevention of Dementia 2008 (LTS'08), are listed in the References. These meetings were convened by the Lou Ruvo Brain Institute to honor the memory of Dr. Leon Thal, a scientist and physician who was an influential leader in the field of AD research before his untimely death in 2007. The LTS'08 was organized in collaboration with the Alzheimer Study Group (ASG), and the Webinar was a joint venture with Alzforum and the ASG. The outline

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below is an executive summary of the deliberations at the LTS'08:

- The Alzheimer's Disease Centers (ADCs) Program of the National Institute on Aging (NIA) should be streamlined and enhanced as Comprehensive Alzheimer's Research Centers, with an expanded mandate to coordinate and support multisite studies on specific research themes.
- The Alzheimer's Disease Cooperative Study (ADCS) Consortium should be augmented with a broader mandate and substantially increased level of funding, to assume new responsibilities. The ADCS investigators and their studies should be linked to community physicians to: 1) facilitate the recruitment of people with increased risk of developing AD, as well as mildly affected patients for clinical trials; 2) support the validation of biomarkers; 3) promote transfers of technology in therapeutic advances and development; and 4) encourage the training and recruitment of new clinical investigators.
- Establish a National Institutional Review Board (NIRB) for the oversight of multicenter clinical trials involving chronic neurodegenerative diseases.
- Develop a drug discovery-development research network consortium to function as a *Virtual Research Pharmaceutical Company* to bridge the gap between academia-based research on the discovery of potential therapeutic targets and early drug-development work (e.g., target validation) typically conducted in a non-academic setting. The objective of this program would be to accelerate the drug-discovery process by enriching the pipeline of potential therapeutic options.
- Create a *National Registry and Database*, as research resource, to meet the multiple needs of the field, such as clinical trials on prevention, the validation of biomarkers, linkage with electronic medical records, imaging, epidemiological studies of risk factors, and other longitudinal studies. The National Registry and Database should be created as part of the restructuring of the NIA's centers program in collaboration with the Centers for Disease Control (CDC) to identify asymptomatic people (either not at risk or at risk for cognitive impairments), as well as people with mild cognitive impairment who have volunteered to participate in research.
- Expand current good clinical practices (GCP) guidelines to standardize procedures across clinical trials.
- Reauthorize administrative costs within National Institutes of Health (NIH) grants.
- Encourage the inclusion of potential biomarkers to supplement clinical efficacy within new drug applications.
- Support the collection of promising neuroimaging biomarkers within clinical care to build the needed databases to confirm their utility and extend their use in clinical trial designs.

- Concerns about tolerability and/or management of adverse events often prolong phase III studies or delay the approval of potentially useful therapies. To address this problem, one solution is to create a new category of drug approval, i.e., Temporary Approval, contingent on aggressive phase IV postapproval monitoring of data on adverse-events efficacy and safety.
- Create an AD drug-development program within the Food and Drug Administration (FDA) similar to the Office of Orphan Drug Product Development.
- Extend marketing exclusivity for a drug as an incentive for sponsors to develop drugs for the prevention of AD and other illnesses that may require lengthy, expensive trials.
- Develop incentives for sponsors of clinical pharmaceutical trials to use and validate biomarkers as part of their clinical trials.
- Encourage the identification of individuals at high risk of AD and with mild dementia for clinical trials through the reimbursement of brief cognitive assessments and AD biomarkers.
- Reimburse dementia health education and social services during initial memory evaluations that encourage participation and retention in clinical trials.

2. Public-policy initiatives: Thinking big

The deliberations of LTS'08 focused on recommendation for public-policy initiatives concerning 5 major governmental agencies that bear responsibilities for AD-related programs. The specific topics under consideration were previously considered at the inaugural Leon Thal Symposium in 2007 [4], and discussed in a Webinar held on October 27, 2008. These subjects centered on recommendations concerning the NIH, the CDC, the FDA, the Centers for Medicare and Medicaid Services (CMS), and the Department of Commerce. One of the key recommendations to emerge from the discussions was the need for increased interactions and collaborations among these agencies. Indeed, many of the suggested recommendations require interagency cooperation, primarily to establish partnerships between academia, healthcare providers, volunteer health advocates, and the private sector.

Five major programmatic changes were identified that could significantly alter the landscape of therapy development and promote more efficient and effective AD research, treatment, and drug development. These recommendations include:

1. Enhance and expand the Alzheimer's Disease Center's Program into *Comprehensive Alzheimer's Research Centers*. The objective would be to streamline the Alzheimer's Disease Center's Program and broaden the scope of activities to include research on interventions, diagnosis, imaging, prevention trials, and other longitudinal studies that require long-term support. There

is an increasing need to identify subjects at high risk of AD for prevention trials and very early in the course of their illness for clinical trials of disease modification. The enhanced Alzheimer's Disease Center's Program should allow more variability between centers by supporting collaborative linkages with other institutions, and thus draw on wider expertise from different locations.

2. Augment and amplify the ADCS as an integral component of the Comprehensive Alzheimer's Research Center, and select participating sites as Clinical Centers of Excellence. These sites would provide data on biomarkers and support services that would link early diagnostic assessments with clinical researchers. In addition, such reorganization would allow community physicians to participate in research to identify at-risk individuals early. They would incorporate and support efforts towards a national registry (discussed below) and the training/retention of new investigators. They would be regionally based, and set up to integrate clinical care with research programs. They could also provide support for infrastructure at sites, loosely modeled on the Early Clinical Drug Evaluation Units (ECDEU), as established by National Institute of Mental Health in the late 1960s. Through this network, academic centers had readied facilities, staffs, and patient populations that enabled quick and cost-effective participation in collaborative multicenter trials implemented by the ADCS Consortium, a central component of the ECDEU infrastructure. Academic centers have traditionally had limited access to community populations. The proposed changes should incorporate aspects of NIH Clinical and Translational Science Awards that provide infrastructure support to expand research to outpatient and community populations. These large, diverse populations are an underutilized resource that could decrease recruitment costs and serve as a subject pool for prevention studies.
3. Establish the NIRB for oversight of multicenter clinical trials for AD. Each clinical trial and each academic site participating in a trial must currently obtain separate institutional review board (IRB) approval, with different and sometimes conflicting guidelines for each site. Many noninstitutional (e.g., private clinics) and some academic sites already use commercial IRBs, providing a uniform regulatory approach without harming research volunteers. The redundancy and inconsistency of multiple IRBs in a multisite trial places a heavy, unnecessary administrative burden on academic investigators, decreasing their efficiency and increasing the costs of clinical trials. Clear guidelines should be developed for the conduct of clinical trials in AD that can be applied consistently across sites and trials. Moreover, this significantly complicates the conduct of multicenter clinical trials, and interferes with minor modifica-

tions that might be warranted by developments in disease knowledge, such as (but not limited to) the handling of patient samples for novel biomarker discovery and validation. The challenges for the Department of Health and Human Services will be to promulgate new regulations, and to amend current policy and policy guidance to potentiate a NIRB.

4. Develop a Virtual Research Pharmaceutical Company to help bridge the gap between academic research and drug development, by allowing different laboratories to participate in various stages of drug development, e.g., medicinal chemistry, drug metabolism and pharmacokinetics, toxicology, proof of concept in preclinical animal models, and ultimately trial design. This virtual entity would alleviate the nearly insurmountable burden of requiring all such disciplines to exist at a single institution, and could fund collaborative projects, leading to broader exchanges of novel ideas throughout the AD research field. Intellectual property issues that restrict progress would need to be addressed. The NIH currently has a number of cross-agency programs to provide resources for animal model exploration, formulation, medicinal chemistry, and toxicology. However, these programs may be insufficient to move new targets identified in academic laboratories forward along the drug-development pipeline. As part of the Virtual Research Pharmaceutical Company, symposium participants recommend modifications of NIH funding policies and limits (such as those placed by the Small Business Innovative Research/Small Business Technology Transfer mechanisms) to create incentives for a virtual program, including administrative cost reimbursement.
5. Build a *National Registry and Database*. A National Registry and Database of aging individuals and those at risk for cognitive impairment is necessary to facilitate more efficient and meaningful randomized trials. Such a registry/database will also lead to a better understanding of changes in the natural progression of the disease. From a public-health perspective, such a registry would also allow better targeting of communication to inform people regarding current knowledge about diseases of aging, prevention strategies, and clinical trials.

Although several organizations could take a productive lead in this effort, a clear mandate resides with the CDC, which has agreed to do surveillance on AD and cognitive dysfunction. Moreover, the CDC has both the experience and the public acceptance needed to encourage mass participation. It should be noted that some participants felt that the establishment of such a registry falls more naturally under the Administration on Aging (AOA), and that collaboration should be promoted between the CDC, AOA, and the United States Department of Veterans' Affairs (VA) in terms of their

inherent resources (knowledge and access to individuals) and as funding sources. In addition, volunteer health advocacy groups and nonprofit organizations such as the Lou Ruvo Brain Institute and the Alzheimer's Association could oversee this type of effort through a network of chapters to facilitate enrollment.

To remove any stigma that might be associated with enrollment, a *National Registry and Database* on aging (to include successful, typical, and impaired aging) should capture the entire spectrum of individuals who would be candidates for interventions. Also embedded in any effort for a National Registry and Database should be a system of prospective cohorts to observe disease incidence (specifically, starting with those who are nondiseased) and parallel systems to observe natural history, consisting of a broad selection of persons with early disease, or a surveillance mechanism (preferably population-based) to identify and enroll new cases and determine factors associated with survival and end results, as well as to provide subjects for treatment trials.

The Federal budget provides appropriations for the CDC to work on projects broadly related to brain health. A *National Registry and Database*, with support from the other organizations and agencies mentioned above, could expand surveillance into areas of cognitive dysfunction, dementia, and general brain health. The VA already maintains a database with a robust information technology core. The addition of spousal participation, with a low barrier for entrance, would broaden the inclusiveness of the registry. Alzheimer's Disease Centers could also collaborate in these registries, particularly if the mandate of the ADCs were *expanded* to include a subset of noncognitively impaired people in their patient populations. Assuming that physicians would enter the names of their patients into the registry, compensation for the administrative costs incurred by physicians would be necessary. Legislative action would be needed to protect the privacy of participants and ensure that registration could not be used to affect negatively insurance coverage or employment.

3. Additional recommendations

In addition to the first four recommendations listed above, participants suggested other policy changes that could have important implications. Recommendations were made to align with the *pay-as-you-go* Congressional budget rules that compel new spending changes not to increase the federal deficit. This caveat means any changes must either be "budget-neutral" or offset with savings derived from existing funds or programs. The recommendations are listed according to the five major topic areas around which the LTS'08 symposium was structured.

3.1. National Institutes of Health

Because the causes of AD in most patients remain largely unknown and because so many clinical trials have failed, a critical need exists for the NIH to expand basic research

efforts elucidating the processes resulting in this condition, and to evaluate pertinent drug targets critically. The NIH should redirect additional funding toward AD-focused R01s, P01s, and K awards, independent of whether or not the investigators have an affiliation with major AD research centers or not.

Although participants of the symposium were uncertain whether this increase in funding should be focused on the NIA or should involve programs that cut across various NIH institutes with a focus on neuroscience, it is clear that the field would benefit from the increased involvement of neuroscientists with diverse backgrounds and areas of expertise.

Another major problem identified with regard to the NIH is reduced productivity because of the administrative burden and bureaucracy associated with the conduct of clinical trials. Because data are needed to quantify the extent of this problem, a number of specific recommendations were offered:

- Expand current GCP guidelines to provide standardized procedures (with flexibility to accommodate special targets, new and improved or otherwise superior procedures and assessments, and regional and corporate differences) across clinical trials. Such changes could, conservatively, double the number of clinical trials currently performed at ADCs.
- Reallow administrative costs to be included in NIH grants. As currently structured, administrative responsibilities are shifted to principal investigators, reducing their productivity.

In terms of existing NIH programs, symposium participants suggested that the insufficient visibility of these programs has not attracted additional funding from other agencies.

- Existing NIH programs should identify gaps in drug development, and then set goals for new targets that need to be identified and the number of therapies that need to be introduced into phase II and phase III studies, and then get a commitment from the NIA to deliver the budget required to meet these targets.
- Insufficient numbers of trainees choosing disciplines that support drug-discovery research (e.g., medicinal chemistry, drug metabolism, and pharmacokinetics) hinder progress in drug development. Hence a manpower study should be conducted to determine the number of trainees needed.
- New types of K-awards (NIH Individual Career Development Applications, or "K-series") should be established to encourage junior investigators to enter into AD research. Training awards should also encourage linkage between community populations and clinical trials. There should be support from the NIH (and other agencies) to require that facilities demonstrate a willingness to develop compliance systems that will allow utilization of CMS funding where appropriate.

3.2. Centers for Disease Control

Recommendations regarding the CDC revolved primarily around the National Registry and Database discussed above.

3.3. Food and Drug Administration

Approval of new treatments has been stymied by a lack of validated biomarkers, and several other treatments have met other regulatory roadblocks. In terms of biomarkers, as the field moves forward in gathering specificity and sensitivity data for proposed mechanisms, there is an emerging recognition that surrogate biomarkers might be useful in the drug-approval process. However, the state of the art suggests that a consensus on surrogate biomarkers is not presently attainable.

A common concern centers on the identification of drug products that will affect plaque loads, Pittsburgh compound B signals, or other pathological features, but not cognitive deficits. Important “biomarkers” will be able to identify the actual presence of disease, or are factors that can be targets of secondary prevention efforts. Thus, such biomarkers would become the focus of treatment. Circularity must be avoided in determining these biomarkers: if observable changes result from the disease process, they may be useful in monitoring disease progression, but would be essentially useless as a treatment target.

The participants of the LTS’08 recognized the FDA’s dual role as evaluator of new therapy safety and effectiveness, as well as an important scientific collaborator in applying new research discoveries to serve the public health. The FDA’s vigorous efforts to promote its Critical Path Initiative, the Biomarkers Consortium, the FDA Intra-Agency Neurology Working Group, and the Alzheimer’s Disease Neuroimaging Initiative are notable examples. Additional recommendations with respect to biomarkers and other regulatory entities to advance therapies for AD include:

- Develop and support the collection and publishing of biomarker results in negative as well as positive studies.
- Accelerate the approval of new therapies contingent on aggressive phase IV postapproval monitoring and data collection to evaluate the safety, efficacy, and sensitivity of biomarkers.
- Create an Office of AD Drug Product Development within the FDA, similar to the Office of Orphan Drug Product Development, to provide incentives for sponsors to develop treatments for rare diseases and establish an advocate within the FDA to whom sponsors can disclose the strengths and weaknesses of their approach.
- Extend marketing exclusivity for a registered drug product as an incentive for sponsors to undertake the lengthy, expensive trials that might be necessary. For example, by starting the clock for exclusivity on the date of approval for a New Drug Application, rather than the date the patent is granted, sponsors could be assured of a reasonable time to market their drug and recoup their development costs without competition from the marketplace.

- Provide tax credits at time of patent publication for some percentage of the clinical-trial costs.
- Provide tax credits and other incentives for sponsors to use and validate biomarkers as part of their clinical trials to encourage the collection of sensitivity data (for validation purposes) on the biomarker, even if the drug product proved unsuccessful as a therapy or fails to achieve marketing approval. One condition of a tax credit or incentive would require that these data are made available to the scientific community, similar to the approach used by the Alzheimer’s Disease Neuroimaging Initiative.
- As part of an investigative new drug application-conducted clinical trial, all treatment and placebo data, including biomarker and genetic information, and outcomes will be placed in a newly established centralized data repository for analysis, to chart the changing natural history of the disease and establish links between altered biomarker and clinical response.
- Promote joint discussions with the FDA, industry, and academics, and establish an organization/agency to help eliminate or circumnavigate legal, regulatory, and other administrative obstacles at their interface.

3.4. Centers for Medicare and Medicaid Services

Because the CMS stands to benefit more than any other agency from the prevention of AD, this agency should encourage and extend existing reimbursement mechanisms that cover healthy aging and cognitive status. Linkage to broadened *centers of clinical excellence* or *comprehensive centers for AD* could further facilitate synergies between the CMS and other government agencies, increasing the government’s return on its investment. Other severe conditions that disproportionately affect older people, such as diabetes and heart disease, increase AD risk and cognitive impairment and can affect their management. Therefore, attention to AD and cognitive impairment is relevant to these other major national health goals.

Although the CMS does not finance specific research studies, demonstration projects are funded. For example, an IRB-approved study was supported that used fluorodeoxyglucose positron emission tomography in people with mild cognitive impairment, paying for magnetic resonance imaging scans, clinical assessments, and frequent neuropsychological testing (Clinicaltrials.gov, NCT00329706). Fluorodeoxyglucose positron emission tomography studies were also approved for some cancers, and some medical devices and interventional procedures were also supported as demonstration projects. A similar mechanism should be used in projects designed to evaluate other biomarkers for AD that could advance early diagnosis and new drug development. Medicare is increasingly consonant with private-insurance companies in terms of the decision-making process. There is a need to document cost savings when research and care are combined, to encourage funding for research studies from both Medicare and

private insurers. Further, CMS data must be made more available to researchers. There are roadblocks and restrictions to access that stifle research efforts to conduct studies using these data. Specifically, the CMS should permit data access such that large samples from which to select appropriate “controls” could be made available in an efficient and responsible manner. This alone would increase a researcher’s ability to conduct studies and achieve relatively unbiased results.

The CMS should expand its mandate to pay for procedures of investigator-initiated clinical trials sponsored by the NIH, specifically for AD. A roadblock to using this funding mechanism is that some clinical sites prohibit the use of CMS funds because of concerns and confusion about compliance issues. In this context, the following recommendations were made: in light of difficulties discerning and complying with CMS regulations (42 CFR 400–413), the CMS must clarify and develop a specific reimbursement vehicle for the coverage of AD patients in clinical research trials. The CMS needs to eliminate copayment for AD patients enrolled in AD treatment and/or prevention clinical trials

Specific recommendations to advance therapy and related studies in AD include:

- Reimburse procedures and laboratory studies that are required for clinical research registries as well as for clinical trials, and implement this process with a limited administrative burden. This change would facilitate the collection of data that could provide new treatments as well as insights into the mechanism and natural history of these major diseases of older persons.
- Include a standardized formal assessment of cognitive status in the “Welcome to Medicare” examination.
- Reimburse brief cognitive assessments appropriate for periodic assessment of high-risk individuals.
- Allocate 1% of Medicare funding to research, on the grounds that research will yield significant cost savings for Medicare. Currently, cognitive problems are under-recognized and misdiagnosed, causing excessive cost and burden. In terms of Medicare funding applied toward improving patient care, these assessments could aid in the early identification of memory and cognitive disturbance necessary for new drug development.
- Reimburse dementia health education at the time of initial evaluation (similar to the current reimbursement of diabetes education), to promote prevention of crises, an understanding of research and treatment options, and an expansion of patient support. This would have the added benefit of enhancing recruitment and retention in clinical trials.
- Reimburse biomarkers in specific situations, e.g., at AD clinical centers of excellence or in targeted programs to assess AD risk. Currently, testing to assess AD risk is not reimbursed, including genetic testing of causative and risk mutations, cerebrospinal-fluid biomarker analysis, and neuroimaging. This is a significant barrier to determining individual risk and appropriate targeting

of prevention trials. Identifying individuals at risk for AD can guide patient and physician behavior, and encourage better control of manageable risk factors such as diabetes, hypertension, and social and physical activity.

- Fund clinical trials and demonstration projects directly, such as a demonstration of the effect of identifying a biomarker on healthcare utilization.

3.5. Department of Commerce

The current system does not provide incentives for companies to develop many promising drugs, in part because the decision-making process is distorted by patent-life issues, which are particularly acute in areas such as neurodegeneration because of the length and complexity of the trials that are required. This situation could be alleviated by extending the patent life for drugs that successfully fulfill the clinical and regulatory requirements for registration and marketing. However, efforts to promote drug companies’ efforts by loosening patent restrictions will undoubtedly face a public (mis)perception issue, impugning that companies are being permitted to maintain higher drug prices. For example, sponsors must calculate the investment costs of bringing a drug to market, and then determine pricing based on the remaining patent life. Extending patent life could lower the cost per prescription, allowing sponsors to negotiate lower reimbursement costs and provide drug products to lower-income people. An initiative is needed that will educate the public regarding the hurdles encountered in pharmaceutical development, particularly in risky and complex areas such as neurodegenerative diseases.

Two changes to patent protection laws and market exclusivity were recommended:

- Restart the patent clock when clinical data are filed rather than when the patent is initially filed on the chemical entity, thus providing an extended period of patent exclusivity.
- Revisit patent decisions around biomarkers. Some biomarkers are patented and protected, which restricts their use in sponsored trials, even when these trials might be useful and appropriate. Unencumbered access to biomarker assays needs to be extended across therapeutic areas.

4. Conceptual changes needed

In addition to suggesting specific policy changes, a number of conceptual changes were explored that could help garner enthusiasm and support from the public, policymakers, and the scientific community. Scientifically, a movement is needed with the aim of redefining AD along the lines of a biological pathway with a slow, degenerative neuropathological process, with potentially multiple etiologies and differentiable endophenotypes. Such a movement would accurately reflect that AD is a decades-long process rather

than a dichotomous event in which a person makes a discernable shift from normal cognition to dementia. Redefining AD in this manner would lead to enormous public-health implications, specifically in terms of awareness, education, and screening. Presently, AD is viewed as a disease of the old. The public-health challenge, and the patient-advocacy challenge, will be to increase the awareness that dementing disorders are not diseases of the aged.

Another obvious extension of this concept is the expansion of the study of AD to include the study of aging in general, emphasizing the importance of prevention of cognitive decline rather than merely the prevention of dementia alone. This broader perspective should result in an important expansion of public and legislative support.

Many of the recommendations that emerged from the symposium would be affected by this shift. In particular, expansion of the group's recommendations to develop a national registry of people at risk for dementia could have broad public-health impact. By including other conditions associated with aging, the registry/database would dramatically increase in scope and encourage participation of other advocacy and special-interest groups. Moreover, the establishment of centers to encompass both research and clinical care for older people would facilitate monitoring for cognitive impairment, the identification of risk factors, treatment of dementia and other memory disorders, and life-long care if dementia is uncovered.

5. Lessons from history

While the delay of disease onset and treatment for dementia are appropriately the current focus of therapeutic research in AD, historical perspectives from other disease areas provide examples where prevention is the only effective therapeutic pathway, with intervention after the onset of clinical disease arriving "too late." Identifying preventative treatments for hypertension, hypercholesterolemia, and bone loss required huge long-term studies and long-term follow-up. The process in many cases began backwards, by first identifying a disease mechanism, clinical marker, or a biomarker, and only later demonstrating clinical benefit. The long road that led to establishing statins as useful for preventing stroke and heart attack began more than 20 years ago, when it was first shown that cholesterol was a reasonable surrogate biomarker for the risk of developing a heart attack or stroke. Subsequently, statins were shown to lower cholesterol, leading to longer-term studies showing that statins also could decrease the morbidity and mortality associated with stroke and heart disease. Yet it is important to remember that statins are not completely effective for the treatment of heart attack or stroke, by which time they are no longer effective. They work only for primary and secondary prevention.

Another important lesson can be extrapolated from experience in treating hypertensive cardiomyopathy. Alzheimer's disease, like cardiomyopathy, can be considered a system failure resulting from a chronic process. Although thiazide

treatment for hypertension is highly effective in preventing cardiomyopathy, by the time a patient has developed cardiomyopathy, treatment with a thiazide is no longer effective. By analogy, the administration of preventative agents before the onset of brain-failure symptoms in AD may provide more effective therapies than treatment of the disease once it has manifested clinically.

In AD, the available data indicate that amyloid imaging or spinal-fluid tests reveal changes that are related to dementia. If it can be shown that a treatment influences either of these markers, it would be reasonable as a next step to ask whether that treatment also influences the rate of cognitive decline, in direct analogy with statins and thiazide in cardiovascular and hypertensive disease. As with the development of statins, this will require a number of years with large numbers of patients and other research volunteers. Such efforts will also demonstrate whether prevention is ultimately required, or if treatments may be more effectively recognized early rather than later in the clinical disease process.

6. Conclusions

Leon Thal was an early proponent of preventive approaches to AD and the necessity for collaboration among stakeholders with a variety of perspectives. Through several meetings and discussions, clinicians, scientists, and others with an interest in AD have formulated several recommendations in Leon Thal's memory that could dramatically alter the AD research and drug-development landscape. If implemented, these changes will establish partnerships to bring together financial, human, intellectual, and political capital, to address what may be the most pressing public-health issue of this century.

Recognizing that the new Congress and Presidential Administration offer an unprecedented opportunity to transform the current system of AD research, drug development, and clinical care, participants at the symposium were charged with formulating actionable public-policy recommendations that are broad, specific, and achievable in a reasonable time. Recommendations must also be economically viable, combining cost savings with desperately needed new funding. In crafting recommendations, it is also necessary to ensure that existing legislative mandates of appropriate agencies are taken into account, rather than simply developing new mandates.

Participants were also reminded that we are not in this alone. International efforts along similar lines are underway in France, Canada, Germany, and Asia. To develop effective strategies for solving the problem of dementia, it will be important to develop international collaborations and seek international funding for many of these initiatives. This paper reflects the outcomes of these considerations and discussions.

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