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

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Executive Summary

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 the key scientific and public policy needs identified in this document will be incorporated by the Alzheimer Study Group (ASG) into a broader National Alzheimer's Strategic Plan (NASP), which will be presented to the 111th Congress and the Obama administration in March 2009. The NASP is expected to include additional recommendations for governance, family support, healthcare and social services delivery.

The need for rethinking and working towards radical changes in the current paradigms for drug discovery and therapy development is mandated by the pending health care crisis. The following sobering statistics underscores the urgency of the public health problem. Currently, an estimated 2.4 to 5.2 million Americans have 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 2050³. 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 these 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 in this paper 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), Webinar on Prevention of Dementia October 2008, and the Leon Thal Symposium on the Prevention of

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Dementia 2008 (LTS'08) are listed in the references. These meetings were convened by 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 Alzheimer's disease (AD) research before his untimely death in 2007. The LTS'08 was organized in collaboration with the ASG and the webinar was a joint co-venture with Alzforum and the ASG.

The outline below is an executive summary of the deliberations at the LTS'08.

- The Alzheimer's Disease Centers (ADC) Program of the National Institute on Aging (NIA) should be streamlined and enhanced as Comprehensive Alzheimer's Research Centers (CARC), with an expanded mandate to coordinate and support multi-site 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. ADCS studies and investigators should be linked to community physicians in order to: a) facilitate the recruitment of people with increased risk of developing AD as well as mildly affected patients for clinical trials, b) support validation of biomarkers, c) promote technology transfer in therapeutic advances and development, and d) encourage the training and recruitment of new clinical investigators.
- Establish a National Institutional Review Board (IRB) for the oversight of multi-center clinical trials for chronic neurodegenerative diseases.
- Develop a drug discovery-development research network consortia to function as **Virtual Research Pharmaceutical Company** to bridge the gap between academia based research on discovery of potential therapeutic targets and early drug development work (e.g., target validation) typically conducted in non-academic setting. The objective of the program is to accelerate drug discovery process by enriching the pipeline of potential therapeutic options.
- Create a **National Registry and Database**, as research resource, will meet multiple needs of the field such as clinical trials on prevention, validation of biomarkers, linkage with electronic medical records (EMR), imaging, epidemiological studies of risk factors and other longitudinal studies. The National Registry and Database should be created as part of the restructuring of NIA's Center's program in collaboration with CDC to identify asymptomatic people (either not-at-risk or at-risk for cognitive impairments) as well as people with mild cognitive impairments who have volunteered to participate in research.
- Expand current Good Clinical Practices (GCP) guidelines to standardize procedures across clinical trials.
- Re-authorize administrative costs within NIH grants.
- Encourage the inclusion of potential biomarkers to supplement clinical efficacy within the new drug application.
- Support the collection of promising neuroimaging biomarkers within clinical care to build the needed databases to confirm their utility and extend use in clinical trial designs
- Concerns about tolerability and/or management of adverse event 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 [Temporary Approval] contingent on aggressive Phase IV post-approval monitoring of data on adverse events efficacy, and safety

- Create an AD drug development program within the 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 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.

Public Policy Initiatives – Thinking Big

The deliberations of the LTS'08 focused on recommendation for public policy initiatives concerning five major governmental agencies that have responsibilities for Alzheimer's disease related programs. The specific topics under consideration were previously considered at the inaugural Leon Thal Symposium in 2007⁴, and discussed in a webinar held on October 27, 2008. These subjects centered on recommendations concerning the National Institutes of Health (NIH), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and the Department of Commerce (DoC). 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, health care providers, voluntary health advocacy and the private sector.

Five major programmatic changes were identified that could significantly alter the therapy development landscape 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 (ADCCs and ADRCs) into **Comprehensive Alzheimer's Research Centers** (CARC). The objective is to streamline the Centers 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 Centers Program should allow more variability between centers by supporting collaborative linkages with other institutions thus drawing upon wider expertise from different locations.
2. Augment and amplify the Alzheimer's Disease Cooperative Study (ADCS) as an integral component of the Comprehensive Alzheimer's Research Center and select participating sites as Clinical Centers of Excellence (CCE). These sites would provide data on biomarkers and support services that would link early diagnostic assessments with clinical researchers. In addition such reorganization will allow community physicians to participate in research identifying y individuals early. They would incorporate and support efforts towards a national registry (discussed below), and training/retention of new investigators. They would be regionally based and set up to integrate clinical care with research programs, and could also

provide support for infrastructure at sites, loosely modeled on the Early Clinical Drug Evaluation Units (ECDEU), which were established by NIMH 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 multi-center trials implemented by the Alzheimer's Disease Cooperative Study consortium (ADCS), a central component of the ECDEU infrastructure. Academic centers traditionally have 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 currently are an underutilized resource that could decrease recruitment costs and serve as a subject pool for prevention studies.

3. Establish a National Institutional Review Board (NIRB) for the oversight of multi-center clinical trials for AD. Each clinical trial and each academic site participating in a trial, currently must obtain separate Institutional Review Board (IRB) approval, with different and sometimes conflicting guidelines for each site. Many non-institutional (e.g., private clinics) and some academic sites already utilize commercial IRBs providing a uniform regulatory approach without harming research volunteers. The redundancy and inconsistency of multiple IRBs in a multi-site trial places a heavy unnecessary administrative burden on academic investigators decreasing efficiency and increasing 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 multi-center clinical trials, and interferes with minor modifications as might be warranted by developments in disease knowledge, such as (but not limited to) handling of patient samples for novel biomarker discovery and validation. The challenge for the Department of Health and Human Services (DHHS) will be to promulgate new regulations, as well as to amend current policy and policy guidance to potentiate a NIRB.
4. Develop a Virtual Research Pharmaceutical Company that would 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. 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 labs forward along the drug development pipeline. As part of the Virtual Research Pharmaceutical Company, symposium participants recommend modification of NIH funding policies and limits (such as those placed by the SBIR/STTR 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 serve as a means to better understand 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 Centers for Disease Control (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 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 U.S. Department of Veterans' Affairs (VA) in terms of both their inherent resources (knowledge and access to individuals) and as funding sources. Additionally, voluntary health advocacy groups and non-profit 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 (this includes 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 non-diseased) and parallel systems to observe the 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 other organizations and agencies mentioned above, could expand surveillance into areas of cognitive dysfunction, dementia and more broadly general brain health. The VA already maintains a database with a robust information technology core. Addition of spousal participation, with a low barrier for entrance, would broaden the inclusiveness of the registry. Alzheimer's Disease Centers (ADCs) could also collaborate in these registries, particularly if the mandate of the ADCs were ***expanded*** to include a subset of non-cognitively impaired people in their patient populations. Assuming that physicians would enter names of their patients into the registry, compensation for 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 impact negatively insurance coverage or employment.

Additional Recommendations

In addition to the top 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*** (PAYGO) Congressional budget rules that compel new spending changes to not 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:

National Institutes of Health (NIH)—Because the causes of AD in most patients remain largely unknown and so many clinical trials have failed, a critical need exists for NIH to expand the basic research efforts elucidating the processes resulting in this condition and to critically evaluate pertinent drug targets. NIH should redirect additional funding for 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 NIH is reduced productivity due to administrative burden and bureaucracy associated with the conduct of clinical trials. While data are needed to quantify the extent of this problem, a number of specific recommendations were made:

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

Related to the existing NIH programs, symposium participants suggested that 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 the numbers of new targets that need to be identified, the number of therapies that need to be introduced into phase II and phase III studies; 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, etc.) hinders progress in drug development. A recommendation was made that a manpower study be conducted to determine the number of trainees needed.
- New types of K-awards (NIH's Individual Career Development Applications, or "K-series") should be established to encourage junior investigators to enter into AD research. Training awards also should help encourage linkage between community populations and clinical trials. Obtain 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.

Centers for Disease Control (CDC)—Recommendations regarding the CDC revolved primarily around the National Registry and Database discussed above.

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

The common concern centers on the identification of drug products that will affect plaque loads, PIB signals or other pathological features but not cognitive deficits. The important "biomarkers" will be able to identify the actual presence of disease, and/or are factors that can be the target of secondary prevention efforts. Thus, such biomarkers themselves would become the focus of treatment. Circularity must be avoided in determining these biomarkers: if there are observable changes which 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 recognize FDA's dual role as evaluator new therapy safety and effectiveness, as well as an important scientific collaborator to apply new research discoveries to serve the public health. 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 to advance therapies for AD include:

- Development and support the collection and publishing of biomarker results in negative as well as positive studies.
- Accelerate approval of new therapies contingent on aggressive Phase IV post-approval monitoring and data collection to evaluate safety, efficacy, and sensitivity of biomarkers.
- Create an Office of AD Drug Product Development program within the FDA similar to the Office of Orphan Drug Product Development, which provides incentives for sponsors to develop treatments for rare diseases and establishes an advocate within the FDA to whom sponsors can disclose strengths and weaknesses of their approach.
- Extend marketing exclusivity for a registered drug product as an incentive for sponsors to undertake lengthy, expensive trials such as those which might be necessary. For example by starting the time-clock for exclusivity on the date of approval for a New Drug Application (NDA), 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 the 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 be a requirement that these data are made available to the scientific community, similar to the approach used by the Alzheimer's Disease Neuroimaging Initiative (ADNI)
- As part of an IND 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 in order to chart the changing natural history of the disease and to 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.

Centers for Medicare & Medicaid Services (CMS)—Because the Centers for Medicare and Medicaid Services (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 CMS and other government agencies, increasing the Government's return on investment. Other severe conditions that affect older people disproportionately, 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.

While CMS does not finance specific research studies, demonstration projects are funded. For example, an IRB-approved study has been supported using fluorodeoxyglucose positron emission tomography (FDG-PET) in people with mild cognitive impairment, paying for MRI scans, clinical assessments, and frequent neuropsychological testing (Clinicaltrials.gov # NCT00329706). FDG-PET studies have also been approved for some cancers, and some medical devices/interventional procedures have also been 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 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 which stifle research efforts to conduct studies using these data. Specifically, 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.

CMS should expand its mandated to pay for procedures of investigator initiated clinical trials sponsored by NIH, specifically for Alzheimer's disease. 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: due difficulties discerning and complying with CMS regulations (42 CFR 400-413), CMS must clarify and develop a specific reimbursement vehicle for the coverage of AD patients in clinical research trials. CMS needs to eliminate the co-payment 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 limited administrative burden. This change would facilitate the collection of data that could provide new treatments as well as insight 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” exam.
- Reimburse brief cognitive assessments appropriate for periodic assessment for 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 addition, Medicare funding applied towards 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 current reimbursement of diabetes education to promote prevention of crises, understanding of research and treatment options, and expanding patient support. This would have the added benefit of enhancing recruitment and retention in clinical trials.

- Reimburse biomarkers in specific situations such as at AD clinical centers of excellence or in targeted programs to assess AD risk. Currently, testing for assessing AD risk is not reimbursed, including genetic testing of causative and risk mutations, CSF biomarker analysis and neuroimaging. This is a significant barrier to determining individual risk and appropriate targeting of prevention trials. Identifying individual risk of AD can guide patient and physician behavior and encourage better control of manageable risk factors such as diabetes, hypertension, social and physical activity.
- Direct funding of clinical trials and demonstration projects, such as a demonstration of the effect of identifying a biomarker on health care utilization.

Department of Commerce (DoC)—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 due to 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, suggesting 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.

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

- Restart the patent clock when clinical data are filed rather than when the patent was 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 the use in sponsored trials even when these assays might be useful and appropriate. Unencumbered access to biomarker assays needs to be extended across therapeutic areas.

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, policy makers, and the scientific community. Scientifically, a movement is needed with the aim of redefining AD along the lines as 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 magnifies would lead to enormous public health implications—specifically on awareness, education and screening. Presently AD is viewed as a disease of the old, the public health challenge, and the patient advocacy challenge, is 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 that would encompass both research and clinical care for older people would facilitate monitoring for cognitive impairment, identification of risk factors, treatment of dementia and other memory disorders, and life-long care if dementia is uncovered.

Lessons from history

While 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 following the onset of clinical disease being “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 by backwards first identifying a disease mechanism, clinical marker, or a biomarker, and only later demonstrating clinical benefit. The long road that led to statins being shown 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 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 do not work conclusively 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 treating hypertensive cardiomyopathy. AD, like cardiomyopathy, can be considered a system failure resulting from a long chronic process. While thiazide treatment for hypertension is highly effective for preventing cardiomyopathy, by the time a patient has developed cardiomyopathy, treatment with a thiazide is no longer effective. By analogy, 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, available data indicate that amyloid imaging or spinal fluid tests reveal changes that are related to dementia. If it can be demonstrated that a treatment influences either of these markers, then it would be reasonable as the next step to query whether that treatment also influences the rate of cognitive decline, as a direct analogy with the statin and thiazide examples 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 may be more effective if recognized earlier in the clinical disease process rather than later.

Conclusion

Leon Thal was an early proponent of prevention approaches for 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 that will 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 frame. 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. In order 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 outcome of these considerations and discussions.

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