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Challenges in Clinical Research on Alzheimer's Disease: Leon Thal's Legacy

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First and foremost, Leon Thal was a clinician. While he was an expert in clinical trials and a superb basic scientist, he was primarily a clinical neurologist. As such, Leon had a real appreciation for clinical diagnoses and the implications of them for patients and families.

Leon was keenly aware of the importance of moving the diagnostic threshold for Alzheimer's disease (AD) to earlier stages, since it was his belief that, if truly disease-modifying therapies were to be beneficial, they would need to be instituted at an early point in the disease process. This ultimately would have implications for treating asymptomatic individuals.

Leon was an early proponent of the concept of mild cognitive impairment (MCI) as a means of identifying individuals at high risk for developing clinical AD at an earlier point in the clinical spectrum. He recognized MCI as the next step for improving our clinical acumen to identify individuals who were going to develop the full picture of AD. Hence, he endorsed and supported the first clinical trial designed to investigate the utility of therapeutics prior to the clinical diagnosis of AD [1].

We embarked on the Alzheimer's Disease Cooperative Study (ADCS) MCI Treatment Trial to assess the utility of therapies at this early stage, and Leon was intimately involved throughout the entire project. This trial also spawned a spate of clinical trials in MCI which have informed the field, not only on the utility of a variety of compounds, but also on the design of clinical trials at this stage in the disease process [2,3,4]. While the ADCS trial was only partially successful, this trial represented the first demonstration of the potential for the postponement of the clinical diagnosis of AD.

Leon recognized, of course, as many did, that the study of MCI was not the ultimate goal of therapeutics in AD. Rather, MCI is likely to be an intermediate phenotype on the way to addressing therapeutics for the general population, and Leon was fundamentally interested in primary prevention. Although, as we have been reminded by Dr. Russell Katz of the US Food and Drug Administration, we may not really mean primary "prevention" in a literal sense; rather, we would be pleased with the delay of onset or slowing of progression of the disease process as realistic intermediate goals [5]. As such, Leon directed the ADCS to perform primary prevention instrument studies in anticipation of therapeutic trials to address the issues of delay of onset or slowing of progression of the disease process.

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Challenges

With this as a backdrop, I would like to address some of the challenges in the field with respect to developing therapeutics that may delay on the onset or slow the progression of AD. It is likely that we will not be able to develop inexpensive or safe therapies, at least initially. It is more probable that the first disease-modifying therapies may incur some degree of risk and are likely to be expensive and, as such, may not be appropriate for the entire aging population. If this were to be the case, then we will need to develop a means for stratifying those individuals at a greater risk for developing the disease and perhaps focus the initial therapies on those subjects with the highest risk profile. Ideally, of course, if an inexpensive and safe therapy were available, its widespread use would be adopted eagerly. However, the reality of the therapeutics of AD suggests that we may have to stratify risks for individuals for the first generation disease modifying therapies.

Prediction Models

Many research groups are trying to develop prediction models for AD. There are several studies designed to refine clinical criteria for the earliest presentation of AD, and possibly move the diagnostic threshold back to earlier stages [6]. However, as we do that, we may run the risk of reducing specificity. That is, we may be able to increase the sensitivity of predicting individuals who are likely to progress from MCI to AD, but in doing so, we may lose some of the specificity of that prediction. Studies on MCI in a community population setting have indicated that, the earlier we make the diagnosis of cognitive impairment, the more likely we are to encounter neuropathological heterogeneity [7,8,9]. However, if we wait until the full dementia syndrome is developed, while we may be more specific with regard to the underlying neuropathologic substrate, but we likely have waited until the point at which a great deal of degeneration has occurred in the central nervous system.

The challenge is to improve sensitivity and specificity, and current thinking in the field suggests that biomarkers may aid in this process. While this is likely true, there are cautions that need to be considered with respect to this approach, as well. Among the most promising biomarkers at present include quantitative measures on MRI, cerebrospinal fluid (CSF) markers for tau and A β , genetic susceptibilities such as those found with apolipoprotein E genotypes, FDG-PET metabolism patterns, plasma markers for A β ratios and proteomic signatures, and molecular imaging such as amyloid imaging with Pittsburgh Compound B (PiB) [10,11,12,13,14,15]. It makes intuitive sense that one or more of these markers coupled with a clinical phenotype may prove very useful.

One proposal to assess this approach would include using the criteria for amnesic MCI (aMCI) of a presumed etiology as the clinical phenotype and biomarkers could be added to increase the specificity that this clinical presentation will progress to clinical AD [16]. Currently, some studies suggest this by documenting higher rates of progression from MCI to AD in those individuals who are ApoE4 carriers or have atrophic hippocampal formations [13,17,18]. Similarly, CSF biomarkers have been shown to predict who is more likely to progress from MCI to AD more rapidly [12]. Markers such as amyloid imaging have suggested an important role for this modality in predicting who will progress, but few longitudinal data are available at present to inform us on this issue.

The real challenge in predicting progression in MCI is to compare these markers to each other. That is, a head-to-head comparison is necessary to validate the predictive utility of each of these markers. Ideally, the true utility of these approaches should be validated in a population-based sample of MCI subjects, since clinic-based samples already have a distorted probability of developing AD in the near future. Consequently, it is difficult to predict from a referral population the true value of these multiple predictors in a more general setting, and, as such,

community-based studies are necessary before these types of recommendations can be adopted for implementation in larger populations.

A similar strategy could be applied to developing prediction models for asymptomatic individuals, as well. Studying MCI is an important strategy, but as Leon had intended, this is not the ultimate goal of our clinical research. We should strive for assessing individuals even earlier in the clinical spectrum, prior to MCI. The same strategy would apply, but now, instead of using aMCI criteria, we might employ an even more subtle clinical presentation such as a modest memory impairment while individuals are still functioning in the normal range. To that, one might consider a positive family history for AD, certain ApoE genotypes, MRI measures, FDG-PET indices, plasma markers, CSF measures, and/or amyloid imaging. However, to make this feasible, the value of each of these clinical presentations and biomarkers would have to be validated in longitudinal studies. These types of investigations require the assessment of large longitudinally followed populations over extended periods of time. These studies are expensive and labor intensive, but necessary. The current funding climate makes these types of studies difficult to conduct and nearly impossible to support financially. At least one or two of these markers may be evaluated in a particular clinical setting, but what is needed is a longitudinal study of thousands of persons with many of these markers available simultaneously.

Alternatively, a more realistic approach might include a stratified screening technique which would entail the utilization of relatively simple screening techniques at first pass followed by more invasive and expensive technologically advanced procedures. For example, perhaps a brief cognitive measure could be combined with a positive family history, genetic susceptibility profile, and a screening blood test such as, a plasma A β ratio. Based on the results of the combination of these markers, subjects could then be stratified for more in-depth assessments using imaging techniques, CSF markers, and other more expensive technologies. Again, however, this approach would need to be validated, preferably in population-based samples to establish their utility as screening techniques for early therapeutic intervention.

To implement these approaches, we will need to shift our focus from small clinic-based assessment to large population-based approaches. In the interim, smaller population-based studies can inform us on the most useful measures to pursue on a larger scale. The current NIH-style research study based on five-year epoch in time makes it difficult to evaluate these various predictive markers. Newer mechanisms for supporting these larger efforts need to be considered.

Ultimately, of course, we are moving toward an approach to individualized medicine. We could envision a situation in which each person has his/her own fingerprint with respect to the likelihood of developing degenerative diseases. This propensity could then be modified with lifestyle interventions or possibly therapies that were disease modifying. We are moving in this direction for chronic conditions such as AD.

Leon Thal was a visionary in our field and championed clinical research designed to modify the diagnostic thresholds for the detection of AD. His work through the ADCS was oriented in this direction, and he had plans of moving the effort to larger audiences, and the field owes him a great debt of gratitude for his leadership toward that goal.

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