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Leon Thal's vision for the treatment and prevention of Alzheimer's disease

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During many informal and formal discussions with Leon Thal during the 5 years before his untimely passing, I came to appreciate his broad strategic vision and analysis of the specific steps necessary to achieve this long-range goal. Like Leon, I am used to writing grants and papers in an “outline style.” Thus, the major elements of Leon's vision are described below: But make no mistake, Leon never saw the field of Alzheimer's research as a series of compartmentalized bits. He saw this field as a tapestry with many threads, all of which contribute to the ultimate final result: prevention of Alzheimer's disease (AD).

1. Basic science

1.1. Understand the underlying pathology

Leon very strongly believed that our underlying understanding about AD sprang from a more complete investigation of the pathology. I always had the impression that this came from his training with Robert Katzman and Robert Terry. Even though Leon was so heavily involved in clinical studies, he continued to co-author papers dealing with pathology.

1.2. Understand the underlying pathophysiology and biochemistry

Leon had a compelling desire to see effective treatments developed, but he realized that such treatments could only arise from more complete understanding of the pathophysiology and biochemistry of AD. Even though much basic research on AD did not directly lead to development of treatments, Leon was a strong advocate for this line of investigation.

1.3. Develop animal models

As a clinical investigator Leon had strong interest in the development of various animal models of AD and neurodegeneration, which would shed light on basic mechanisms and which could be used for studying effects of proposed treatments.

1.4. Develop treatment candidates and test them on animal models

Of course, as a clinical investigator seeking new treatment candidates for human studies, Leon kept a very sharp eye on preclinical studies. I was always impressed with his interest and knowledge concerning the basic biochemical, pathologic, physiologic, and pharmacologic mechanisms of AD and of proposed treatments. Leon excelled in seeing the “big picture” and had a hunger for new knowledge that had any relevance to developing AD treatments. I can remember being amazed hearing him discuss and debate basic immunologic or biochemical mechanisms and the interpretation of such experiments with basic scientists, relevant to selection of treatment candidates for human studies.

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1.5. Select treatment candidates for human studies

As Director of the Alzheimer's Disease Cooperative Study (ADCS), Leon had a unique charge: to help identify potential new treatments for ADCS clinical trials. His broad interests and knowledge gave him a unique platform to see the big picture and to work with basic scientists at universities, the National Institutes of Health (NIH), small companies, and the big pharmaceutical companies to provide advice (he served on advisory boards for almost all companies) and guide selection of new treatment candidates for ADCS.

1.6. Develop appropriate biomarkers (blood cerebral spinal fluid, imaging) to monitor progression in clinical trials

It was in this area that I came to first know Leon. After a background in nephrology and biochemistry research, I became involved in nuclear magnetic resonance (NMR) in 1980, and then NMR became magnetic resonance imaging (MRI). During the late 1980s I decided to focus on AD. In part because my parents were living in San Diego, I visited University of California San Diego (UCSD) often and made efforts to interest Leon in imaging. Only during the late 1990s, around the time that Neil Buckholz organized the National Institute on Aging Biomarkers of AD meeting, did Leon begin to recognize that imaging could be used to monitor the progression of AD, that methods could be used to perform imaging in multisite trials, and that the NIH and industry would bear the expense of imaging as a result of the recognized value. This led to his growing interest in the work I was doing as well as that of many others. Leon invited me to use MRI in the ADCS Valproate trial (principal investigator, Pierre Tariot), and at around the same time, he agreed to join me in pursuit of a project that became the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Clinical

2.1. Understand the clinical phenotype and subtypes

Despite how busy Leon was with his basic science laboratory (he continued to be the principal investigator of an RO1 grant that supported this lab), Chair of the Department of Neurology, Director of ADCS, and countless other responsibilities, Leon never gave up his clinical practice, which he believed kept him grounded in understanding the presentation and progression of AD. As my mother began to develop memory problems (in her late 80s), Leon agreed to take her on as a patient. When she last saw Leon (a few weeks before his accident), he gave her a kiss goodbye, and she was very proud of this sign of affection.

2.2. Develop standardized methods for assessing subjects for clinical treatment trials

Of course, developing standardized methods for clinical treatment trials in AD is the heart of what ADCS does, and Leon was devoted to this topic. However, he clearly recognized and emphasized the limitations of these methods, especially the use of the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog), but he also recognized that "this is all we have." He was a strong advocate for the development, testing, and validation of improved methods.

2.3. Developing clinical infrastructure for multicenter clinical trials including clinical evaluations and biomarkers

Leon's major legacy (aside from the memories that his family and friends have of him) is the ADCS and the huge impact that this organization has had on the field. Without question, ADCS sets the standard for performing ADCS clinical trials and continues to do treatment and methodology studies. The long-term impact of this will ultimately lead to development of effective treatments.

2.4. Conducting treatment trials in patients with AD

I had the good fortune to be on many of the “Thursday afternoon ADCS teleconferences” where Leon would be sitting in a conference room in San Diego, with the ADCS staff around him (including Jackie Bochenek, Ron Thomas, Antony Gamst, Adam Fleischer, the study monitors, and the ADCS staff) while successively there would be 30-minute teleconferences on valproate, docosahexaenoic acid (DHA), ADNI, and many others (including mild cognitive impairment [MCI], huprazine, instrument trials, etc, that I never attended). This was the way that Leon involved himself in the nuts and bolts of each study including site performance, recruitment, data capture, quality control, side effects, institutional review board approvals, budgets, and the list is endless. Somehow he always seemed to have it all in his head or in a printout within 5-second grasp.

2.5. Conducting trials in MCI

Of course, with Ron Peterson, the ADCS performed the MCI trial. Leon strongly believed that we needed to explore treatment at the earliest stage of the disease. Even though the MCI trial with vitamin E and donepezil did not have a huge impact on treatment of MCI, Leon thought that the major accomplishment was “proof of concept” that such a study could be enrolled and performed, and many lessons were learned that would help with future studies on MCI and nondemented populations.

2.6. Prevention trials

As incredible as it might seem, given the above, Leon had energy to think “really big” and closely followed the various prevention trials including Alzheimer's Disease Anti-inflammatory Prevention Trial and Ginkgo. He was working with Bruno Velas on a prevention trial in Europe and helped focus the Lou Ruvo Institute in Las Vegas on prevention efforts. Leon clearly did not think it was too early to be planning such studies.

3. Political, Social, and Economic

3.1. Through leadership, mobilize the collective energies of the overall community, including patients, their families, private donors, foundations, government, and industry

Leon was extremely active in the national and local San Diego Chapter of the Alzheimer's Association. He was extremely active in university affairs including the Search Committee for the Dean of UCSD and a search for his own successor (he had hoped to step down as Chair to focus more on research). He was chosen by Governor Schwarzenegger to serve on the Board of the Institute for Regenerative Medicine because Leon had a strong scientific interest in stem cells.

Finally, on a very personal note, I felt extremely fortunate to develop a close relationship with Leon during the few years before his accident. We spoke on the telephone weekly and often exchanged many e-mail messages each day. We shared a common background (Jewish upbringing in Brooklyn NY, wonderful relationships with our fathers, interest in science from an early age, great marriages to fantastic women), and I hugely enjoyed interacting with this guy who had even more passion for the work and who was working harder than I. I said to more than one friend, “When you play tennis with a real pro, it elevates your game. Working with Leon is like having your serve come back to you at 150 miles/hour.” He was also incredibly and unusually attentive and kind to everyone whom he interacted with. His death shocked me on the scale of my own father's passing. After his accident, I learned from his friends that when he went jogging or hiking, he picked up roadside trash in a plastic bag. I have taken to doing this as a way of remembering this incredibly remarkable person.

In conclusion, once Leon joked to me, “Mike, there is only one problem spending your career on Alzheimer's clinical trials.” In response to my “What's that?” he retorted, “Nothing works” followed by a laugh. Leon would hope that some of the ideas described above help, would add a few more threads, and possibly even inspire some new young investigators to find something that works.