

Leon Thal and the Alzheimer's Disease Cooperative Study

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Leon J. Thal MD, 1944 to 2007

Leon J. Thal died on February 3, 2007 while piloting his airplane. He was 62 years old and a professor at the University of California at San Diego (UCSD) where he directed the UCSD Alzheimer's Disease Research Center. He received numerous research awards, contributed to the scientific literature, and served on the editorial boards of several journals including the editorial advisory board of *Current Alzheimer Research*.

His transcending impact on Alzheimer's disease (AD) is as the founder and leader of the National Institute on Aging (NIA) Alzheimer's Disease Co-operative Study (ADCS), a consortium of mainly academic centers that investigate AD therapeutics. Leon Thal in effect founded the era of modern therapeutics for AD and developed a clinical trials infrastructure that advanced the methods and knowledge of how to test drugs.

The ADCS had its origins in the NIA-Warner Lambert Pharmaceuticals Company-Alzheimer's Association-funded tetrahydroaminoacridine (THA) trial of the mid-1980s. At the time, there were exaggerated claims, publicity and grassroots political demands that tacrine (known as THA) -- a cholinesterase inhibitor then being touted as a treatment that would literally reverse dementia -- must be researched by the government and made available to patients. Leon and colleagues had done work in the late 1970s and early 1980s that provided the evidence that the cholinesterase inhibitor physostigmine enhances cognition, attention and arousal in AD patients; and they had developed a multicenter protocol relying on dose-titration and enrichment of the trial sample to maximize clinical response in order to pursue physostigmine further.

These methods became the framework for the NIA-funded tacrine trial, a trial that yielded less than unequivocal therapeutic results and more controversy. But it was enough to establish the feasibility of AD trials on a number of levels [1] and to allow the development of tacrine to continue in the hands of private industry.

The outcomes and the realization that dosage titration and enrichment as methodology were not practical, that short-term trials were not compelling, and the surprise (at the time) that a brief cognitive assessment scale was actually more sensitive than a clinician's global assessment (the original primary outcome), provided the impetus for the development of clinical trials methods and changed the dementia therapeutic culture to one focused specifically on Alzheimer's disease, mechanism-based pharmacology, and cognitive improvement.

There was now a willingness to test drugs for AD and the tacrine trial sites were the nidus that Leon Thal molded into the ADCS in 1991. Since then there have been four successful funding cycles. The contributions that Leon Thal and the ADCS made to the field were broad and great. By undertaking trials of drugs that others would not do because of limited commercial value, lack of licensing protection, or because the science was too edgy, Leon Thal and the ADCS demonstrated a "can do" feasibility, advanced the field, showed what works and what doesn't, and modeled how clinical trials could be done.

During the first 5 year cycle -- using vitamin E and selegiline as potentially neuroprotective, antioxidative agents -- the ADCS developed new methodology using as outcomes, not *change* on rating scales, but *time* to an illness milestone such as nursing home placement or death. The demonstration of the concept of "survival trials" in AD -- even though it was with moderately to severely impaired patients -- demonstrated a practical utility for the design for future mild cognitive impairment and primary prevention trials [2]. The trial had immense public impact causing physicians to change their prescribing, to think of vitamin E as specific therapy for AD, and the soybean processor Archer Daniels Midland to broadly advertise vitamin E's merits. Unfortunately, there were no follow-up or confirmatory trials by others until the ADCS took on mild cognitive impairment (MCI) in 1999 in the Memory Impairment Study (MIS) [3]. Here the "survival outcome" was time until the onset of dementia and vitamin E was compared to donepezil and placebo. Notably, before the ink was dry on the protocol manufacturers of other drugs had incorporated elements of the MIS design in their MCI trials.

Also in the first cycle, AD trials instruments were advanced with the development of versions of cognitive, activities of daily living, quality of life, and global outcomes that were rapidly appropriated by industry even before the validation studies were completed and used by industry ever since. Such was the enormous influence of Leon Thal's ADCS on the field.

He was willing to take on trials to assess best and relevant treatments for agitation and aggression in AD by comparing haloperidol with trazodone, placebo, and cognitive behavior therapy, and valproate with placebo, recognizing and demonstrating the difficulty of this clinical problem. A trial of melatonin to treat diurnal rhythm disruption and nocturnal agitation legitimized these symptoms as therapeutic targets.

With the extraordinary interest in the mid-1990s in estrogens and anti-inflammatories as both putative cognitive enhancers and neuroprotective agents based on epidemiological research, Leon and the ADCS moved to try to demonstrate the concept with focused longer-term clinical trials of conjugated equine estrogens, prednisone, and later non-steroidal anti-inflammatories. The outcomes here foreshadowed the difficulties ahead in these approaches. Similarly, the potential for cholesterol and homocysteine lowering as therapeutic approaches led to trials to directly test simvastatin and B vitamins.

The trend continued in the ADCS's fourth funding cycle, with ongoing and planned trials of valproate and lithium as "anti-tau" agents, intravenous immunoglobulins as broadly based anti-inflammatories, anti-amyloid beta approaches and docosahexaenoic acid (DHA), an omega-3 fatty acid, as an antioxidant. Leon Thal created and led an organization that through his design, addressed important AD therapeutic issues that others could not, made an impact demonstrating what works and what doesn't, and in so doing allowing people to make informed decisions, keeping them a bit safer and healthier than they would have been otherwise.

Table 1. Selected Trials from the Alzheimer Disease Cooperative Study, 1991 to 2007, Leon Thal, Principal Investigator

Protocol	Dates
Vitamin E and Selegiline	1992-1995
Instrument protocol (English and Spanish)	1993-1995
Haloperidol and trazodone for agitation	1994-1997
Prednisone as an anti-inflammatory	1995-1998
Conjugated equine estrogens	1995-1999
Melatonin for sleep disturbance	1997-2000
Vitamin E, donepezil for mild cognitive impairment	1999-2004
MCI instrument development	1999-2004
Naproxen and rofecoxib as anti-inflammatories	1999-2001
Valproate for agitation	2000-2002
Instruments for prevention trials	2002-2006
Cholesterol-lowering with simvastatin	2003-2007
Homocysteine reduction with B vitamins	2003-2007
Valproate for neuroprotection	2003-2009
Anti-oxidant, DHA	2007

Although the development of AD drugs has proved harder than most of us thought it would be when the ADCS was formed, Leon asserted a sense of inevitable optimism, that we know enough about the illness, and learning more, so that meaningfully effective therapeutics are within our ken if we are willing to look. As inevitable as future advances are,

they somehow do not seem as certain without Leon Thal. No other person could have accomplished as much as fast. I will miss him. With every future ADCS decision we will collectively wonder, "What would Leon have done?"

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