

**Statement of
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Before the
Subcommittee on Oversight and Investigations
Committee on Veterans' Affairs
U.S. House of Representatives**

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Mr. Chairman and Members of the Subcommittee:

Though new to VA, I have been a researcher in Alzheimer's disease (AD) for nearly 20 years, with a primary interest in developing strategies for the treatment and prevention of the disease. Currently, I am directing a multi-center clinical trial to determine if lipid-lowering drugs slow the progression of AD. This is run with a consortium of Alzheimer's Centers around the country, and includes several other VA sites.

One of the first observations to support the idea that the use of cholesterol lowering drugs could have benefits in this population was made by Dr. Benjamin Wolozin, a physician at the Edward Hines VA Medical Center (VAMC) in Hines Illinois. Through record review, he determined that the prescriptive use of certain drugs known as "statins" was associated with lower risk of AD. While observational studies only give a hint about potential benefits, we are now conducting a rigorous randomized trial that is designed to determine if one of these agents will slow disease progressing in patients with mild to moderate AD.

The Alzheimer's Disease Research Center, located at the Bronx VAMC and at Mount Sinai School of Medicine in New York City, which I direct, provides an infrastructure to use state of the art clinical assessment of patients and to offer patients the opportunity to participate in cutting edge research. One of the most valuable resources at our medical center is the brain bank for AD and other cognitive disorders. This resource permits us to conduct clinical-neuropathological correlations to determine the changes that occur in the brain with aging and disease. Because of the careful clinical diagnosis with electronic

record keeping at VAMCs, we are able to maximize the very generous contribution of our volunteers to compare detailed information from their medical records with subtle and microscopic changes at the cellular level to get a clearer picture of the biology of AD. This resource has led to an important observation about cell loss. We know that AD is associated with neurofibrillary plaques and tangles. From these studies we can surmise the areas of the brain that appear to deteriorate first. For example, the areas known as the entorhinal cortex and the hippocampus appear to deteriorate first. These brain areas are involved with memory and learning, and we now know that serious impairments in memory may predict AD several years before the disease can be diagnosed. We also know there is definite loss of neurons in AD, but in healthy elderly individuals and in very mild cases, there are apparently normal neurons that undergo the initial stages of tangle formation. Furthermore, the loss of neurons is limited, compared to AD cases. This is important because it suggests that we may be able to “rescue” neurons at this mild stage and therefore we may focus our attention to treatments at this early stage.

VA has a long history of research in AD. The very first multi-center study for an approved treatment for AD was published in the New England Journal of Medicine under the leadership of a VA physician, Dr. Kenneth Davis, the former Chief of Psychiatry at the Bronx VAMC. This work made a long-standing contribution in that it provided the methodology for conducting multi-center studies for testing new treatments for AD. That methodology is still used today. In particular, the very test used to determine drug efficacy in dementia in nearly all pivotal studies is the Alzheimer’s Disease Assessment Scale (ADAS), which was developed at the Bronx VAMC. Though this test was published nearly two decades ago, it remains the most commonly used assessment in clinical trials for AD in the U.S. and around the world.

Many renowned VA AD research colleagues, who have been in the field for years, have made important contributions. From “bench to bedside” is the challenge for VA research, and it is met in the research of Mark Tuszynski, MD, PhD, (San Diego VA Medical Center), through his pioneering work examining

fibroblasts and, more recently, other types of cells. These cells have been transduced to express genes for growth factors such as nerve growth factor (NGF), and then transplanted into the brain. This work started about a decade ago with funding from VA and has proceeded to show that grafts could reverse memory deficits resulting from lesions associated with AD pathology. This work subsequently advanced to studies in monkeys, and, two years ago, to the first clinical trial of gene therapy in patients with AD, who are transplanted with their own fibroblasts, which have been transduced to produce NGF. Much of the preliminary work is attributed to the published work of Dr. Tuszynski, and this interventional approach provides great hope for effective treatment.

While finding cures and preventions are important, even our best efforts will leave many with AD. VA researchers have done cutting edge research to define and maximize patient independence and comfort. To that end, VA researchers have described the standards of determining “decision making” capacity in patients with AD. The rigorous research conducted lays the foundation for determining the best way to evaluate patient ability to participate in clinical and research decisions.

A report of the National Ethics Committee of the Veterans Health Administration (lead author: Dr. Ladislav Volicer, Edith Nourse Rogers Memorial VAMC, Bedford Massachusetts) summarizes the empirical data on the important role of families in making decisions for patients with impaired capacity. The report found that even when asked prior to the onset of any limitations due to illness, patients prefer that a family member make decisions for them, and often prefer this to advanced directives. Therefore, an important conclusion from this report is that we need to make decisions that truly meet patients’ needs and desires. The report also contains specific recommendations for the advance proxy planning process.

In summary, the success of AD research in VA is the result of a series of partnerships. These partnerships begin with the generous spirit of the veterans who volunteer to participate in VA clinical research. They include the melding of clinical resources, such as the electronic medical record system and centralized

databases, with the outstanding curiosity of VA researchers, and would not be possible without the research resources to make the best use of the scientific opportunity and the commitment to deliver the best of care.