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### Alternative Models for Drug Discovery in Alzheimer's Disease

Alzheimer's disease is described as a progressive dementia associated with the extracellular deposits in the brain of a garbage protein,  $\beta$ -amyloid ( $A\beta$ ), and the intracellular deposits of tangles. The vast majority of the patients develop the disease in old age while a small portion have an early onset, familial form. Since the 1970's it has been generally assumed that the dementia seen in the two forms is due to the neurotoxicity of the  $A\beta$ . With the purification and sequencing of  $A\beta$  in the 1990's investigators were able to identify the mutations associated with the familial forms. A number of laboratories transfected mice with these mutated genes. Since these animals exhibited many of the pathological and clinical manifestations of the late onset disease, they have been used to screen for new therapeutic agents. Unfortunately, all 244 drugs identified in these models have failed in clinical trials in elderly patients. Work from my laboratory has suggested that plaque deposits of  $A\beta$  rather than causing the dementia is merely a biomarker for a decline in the capacity of the endoplasmic reticulum (ER) in the cells to catalyze the posttranslational processing of 40% of cellular proteins, including those synaptic, membrane proteins required for a functioning memory. This paradigm is based on our observation that in the CSF all  $A\beta$  is normally N-glycosylated and bound to ER proteins, ERp57 and calreticulin. These data suggest a new direction for drug discovery in which agents are screened for their ability to increase the levels in cell lines of fluorescently labeled components of the ER post-translational pathway. The development of these cell lines would permit rapid screening for potential therapeutic agents in plate readers.

### Biography

Jordan L. Holtzman, M.D., Ph.D. is Professor, Departments of Pharmacology and Medicine and Division of Environmental Health Sciences, University of Minnesota, Minneapolis, USA. He was graduated from University of Chicago, the Pritzker School of Medicine in 1959. He completed internship from University Ill Rsc/Ed in 1960.

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