

Public Lecture by Dr. Douglas R. Galasko
New Treatments for Alzheimer's Disease
September 18, 2002 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Background:

In Alzheimer's Disease (AD), the brain undergoes shrinkage (atrophy), due to loss of nerve cells, or neurons. Characteristic changes under the microscope consist of plaques and tangles. Plaques are located outside nerve cells, and start out as deposits of a molecule called beta-amyloid (A_β). They enlarge and develop into a dense core and a less dense periphery, with a rim of inflammatory brain cells and degenerating processes (branches) of nerve cells, called neurites. Amyloid may be toxic to nerve cells if it aggregates (clumps together). Tangles (also called neurofibrillary tangles, or NFT) are inside nerve cells, and are insoluble clumps of a molecule called tau. Tau normally helps to form the skeleton that gives shape to nerve cells.

Symptoms of AD, e.g. memory, can be improved slightly by cholinesterase inhibitors such as donepezil, rivastigmine or galantamine. These medications don't stop the progressive degeneration. New approaches to treat AD aim to slow progression of disease, or delay or prevent its onset.

Early diagnosis is important, because it enables treatment to begin while brain function is relatively intact. A stage of very early "pre-Alzheimer's Disease" has been described, and is called Mild Cognitive Impairment (MCI). Patients with MCI have memory difficulty, but very little impairment in daily activities. Advances in early diagnosis include (1) detailed tests of memory, (2) Imaging of brain structure eg by MRI, or function eg by SPECT or PET. Volumetric MRI can detect atrophy in AD, for example in the hippocampus, which is important in memory and learning. Recently, PET has been used to image brain amyloid deposits (3) Tests of blood and cerebrospinal fluid (CSF) include measuring amyloid and tau in CSF. These differ in AD compared to non-demented elderly controls.

New approaches to treatment:

A. Ideas for treatment come from two main sources:

- Risk factors and protective factors: usually identified in epidemiological (observational) studies. There are many biases and false positives in these types of studies, and clinical trials remain the definitive tests of treatment. As examples, estrogen, NSAIDs (medications such as ibuprofen), anti-oxidant vitamins and cholesterol-lowering drugs appear to be protective in observational studies.

- Understanding the biology of AD: e.g. pathways of amyloid production and removal by the brain; genetics of AD. Three genes are associated with early onset familial AD, and all alter A_β production to favor longer forms of more toxic, stickier A_β.

B. Treatment based on risk factors/protective factors:

- Estrogen: negative trial in slowing progression of AD

- Anti-oxidant vitamins: MCI trial still in progress

- Cholesterol-lowering: statins will be studied in AD starting in 2002

- NSAIDs: negative trials of naprosyn and celecoxib in slowing progression. Prevention trial ongoing.

C. Treatment approaches based on mechanisms of disease:

1. Amyloid:

- Decrease production: block the molecular scissors (secretase enzymes) that cut A_β from APP.

- Improve removal: antibodies against A_β can bind to A_β and make it easier for scavenging cells in the brain to recognize it. A clinical trial of immunization against A_β (started in Oct 2001) was halted in Feb 2002 because about 8% of patients developed side effects resembling meningitis.

2. Oxidative damage:

- anti-oxidants e.g. vitamin E and others

3. Excitotoxicity: damage from over-stimulated nerve cells may set up a 'chain reaction' of damage:

Memantine blocks glutamate, an excitatory chemical, and may slow the progression of severe AD.

4. Inflammation:

- NSAIDs don't appear to slow AD. However, recent work shows that some NSAIDs, in high doses, selectively decrease A_β42.