



# Alzheimer's disease

## Its Cause and Impact of Treatment

Very soon, physicians will treat Alzheimer's disease (AD) much in the same way that diabetes and hyperlipidemia are treated. In 2005, in *Archives of Neurology* (14), Dr. Dennis Selkoe of Harvard University, characterized a consensus—the culmination of 20 years of scientific research on AD pathophysiology—that the cause of AD is either excessive neuronal production or reduced clearance of beta amyloid in the brain.

At the basic science level, AD transgenic mice have helped connect the neuropathology of AD to its clinical dysfunction. Dr. Frank LaFerla and others (1,13) have shown that reducing the beta amyloid production in AD transgenic mice reduces the production of AD neuropathology and delays the development of cognitive impairment. Dr. Richard Dodel used transgenic AD mice to show that a single intra-peritoneal injection of antibodies directed against beta amyloid reduced the free-floating beta amyloid brain levels by clearing it into the blood, and improved short-term memory performance in a dose-dependent fashion within three days (4). Dodel's studies showed no change in the neuritic plaque content of beta amyloid after a single intra-peritoneal injection of anti-beta amyloid antibodies, which means that the free-floating beta amyloid outside of neurons significantly impairs brain function.

At the clinical science level, agents which lower beta amyloid production or increase its clearance reduce the risk of developing AD by up to 75% (9,18). These agents include the statins, aspirin and eight non-steroidal anti-inflammatory drugs (2,5,17). From epidemiological research, the prevalence of AD in India is 1/3 that of the USA even though the distribution of the major genetic AD risk factor, the apolipoprotein E4 allele, is the same in the two countries (3,7,16). The high intake of curry in India is proposed to explain lower AD prevalence there. Furthermore, curcumin (an active ingredient in curry), when fed to transgenic AD mice, reduced free-floating and neuritic plaque-bound beta amyloid levels by approximately 50% (12). Human clinical trials are underway to examine the impact of curcumin in AD.

At the International AD Conference in Geneva in April, 2006, Elan Pharmaceuticals, who has conducted three year clinical trials in AD patients receiving an antibody that binds to beta amyloid, reported three important findings. First, AD patients treated for between months and years who then died and went to autopsy showed a marked reduction in beta amyloid in their brains—the longer the treatment, the greater was the reduction. Second, the rate of cognitive decline in treatment vs. control patients was slowed by 30—50%. Third, the rate of atrophy in treatment vs. control patients was significantly reduced. These findings support the hypothesis that excessive beta amyloid in the brain is a very important component of AD pathophysiology and clinical expression. Since it takes about 30 years for beta amyloid to accumulate before AD symptoms appear, it is possible that significantly lowering beta amyloid levels will delay AD progression for years.



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*This consensus regarding the pernicious role of beta amyloid greatly simplifies AD treatment. Similar to lowering cholesterol to prevent heart disease and stroke, and lowering blood glucose to control diabetes, lowering brain beta amyloid levels delays AD progression.*

Quite a few agents lower beta amyloid in the brain, including some of the statins (Lipitor, Zocor, Pravachol, etc.) (6), some of the non-steroidal anti-inflammatory medications (ibuprofen, sulindac, indomethacin, R-flurizem, etc.), aspirin (which reduces aggregation of beta amyloid into fibrils), curcumin, as well as the cholinesterase inhibitors (Aricept, Razadyne, and Exelon) (8,10,11).

With this recent knowledge, it is possible to begin formalizing a best practice approach to AD management. Useful tools to implement this approach are listed in parentheses and can be found for healthcare professionals at [www.mccare.com](http://www.mccare.com). The six basic steps are:

1. Identify AD risks and select safe treatments to reduce them.
2. Select what age to begin annual screening for cognitive or functionally related impairment. Cognitive changes due to cerebrovascular disease begin at 50 years or older, while those due to AD begin about 58 years or older.
3. Diagnose it correctly (FAST Staging).
4. Initiate AD treatment as early as possible to reduce beta amyloid brain levels.
5. Measure treatment effect on delaying AD progression and adjust appropriately (FAST Staging and MCI Screen).
6. Distinguish between decline due to AD progression and decline due to other reasons, and treat identified problems effectively (FAST Staging).

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