

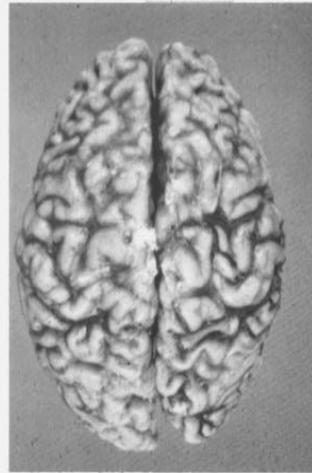
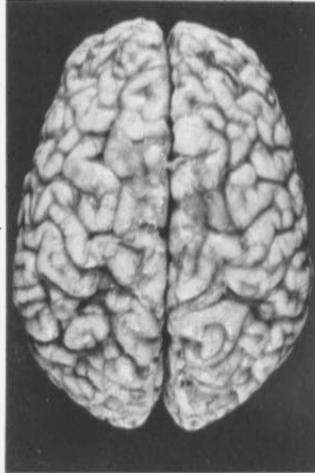
Dementia Treatment and Prevention

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Dementia

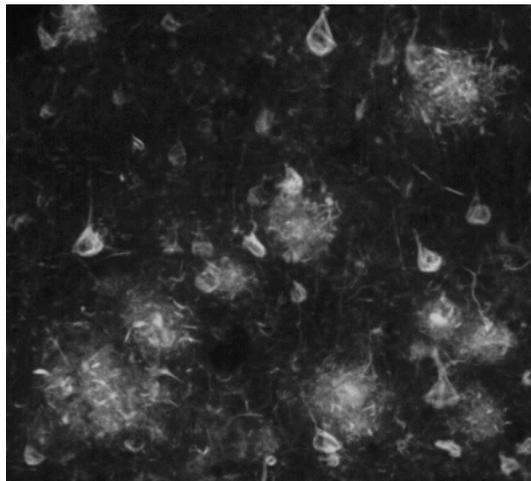
- Dementia is a major public health concern
 - Prevalence
 - Chronicity
 - Caregiver burden
 - Financial costs

There are no cures for the neurodegenerative dementias.



Brains of a normal individual (l.) and an Alzheimer patient (r.). Convolutions in the Alzheimer brain show considerable shrinkage.

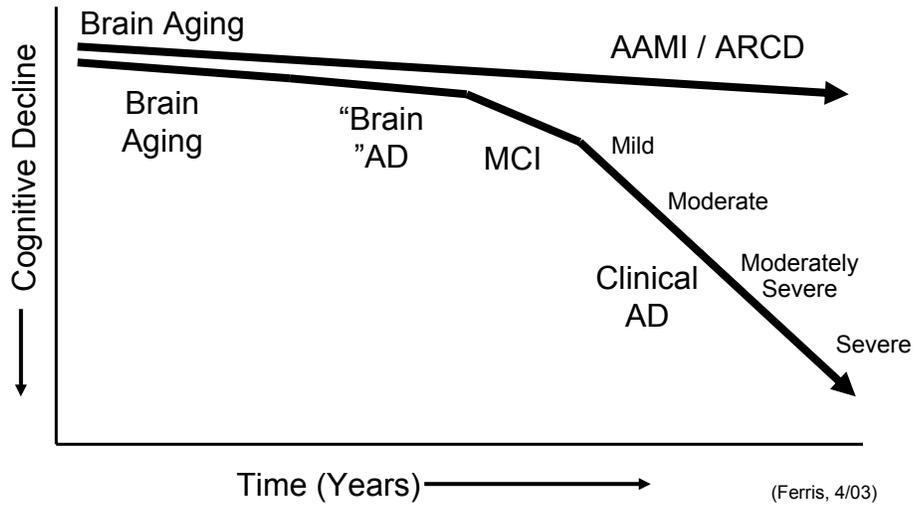
Alzheimer brain - microscopic



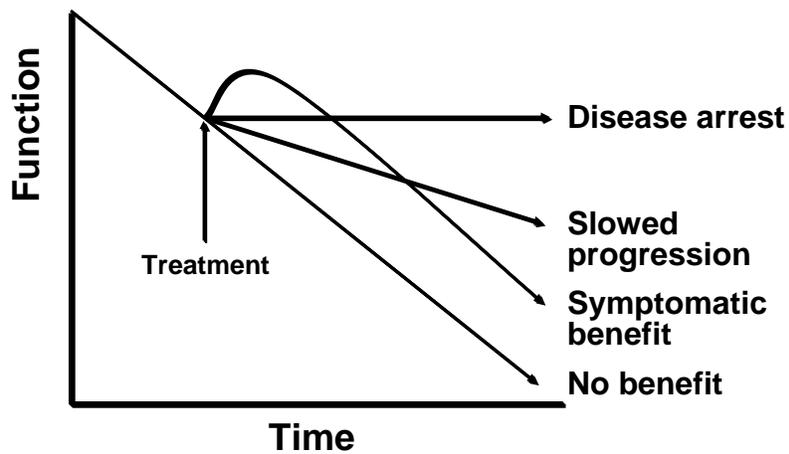
The hallmarks of Alzheimer's pathology are amyloid plaques and neurofibrillary tangles, both of which are visualized here with thioflavin-S labeling. Neurofibrillary tangles are seen here as "flame-shaped" structures, and often fill the neuronal cell body which they occupy. Amyloid plaques are seen as diffuse and round fibrous structures.

From the Basic Human Brain Research Laboratory at Northwestern University's Alzheimer's disease Center: <http://www.brain.nwu.edu/gallery/P&Tpicture.htm>

Course of Aging, MCI and AD



Possible Treatment Outcomes



Dementia

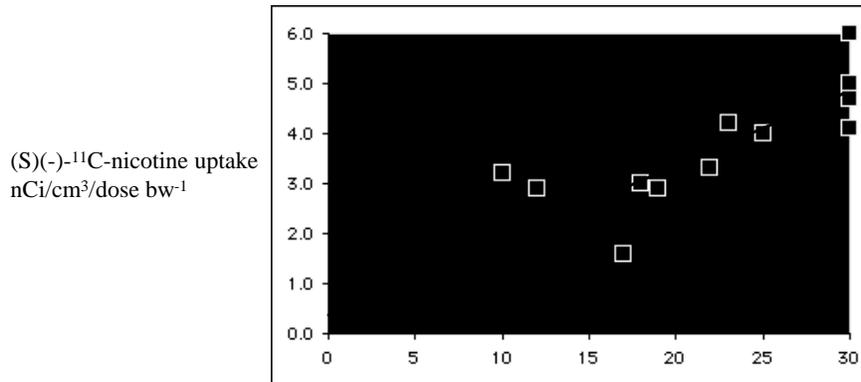
- Clinicians prescribe various pharmacotherapies to alleviate symptoms and delay disease.
- Currently 5 drugs have FDA approval for treating and managing dementias.

Therapeutic approaches based on pathogenic mechanism

- Cholinergic deficiency
- 1st generation:
- 2nd generation:
- Cholinesterase inhibitors:
 - Tacrine
 - Donepezil
 - Galantamine
 - Rivastigmine

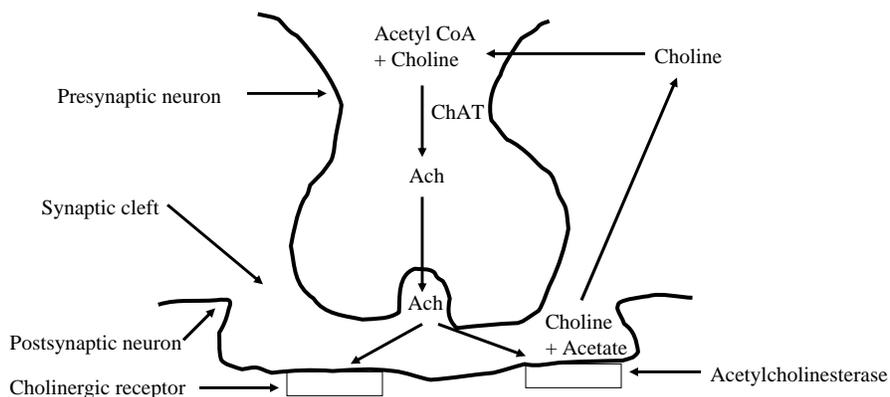
Correlation of cognitive function with cholinergic dysfunction

Comparison of ^{11}C -nicotine uptake as assessed by PET and the MMSE¹



¹Reprinted with permission from Nordberg A. Biological markers and the cholinergic hypothesis in Alzheimer's disease. *Acta Neurol Scand Suppl.* 1992;139:54-8. PMID: 1414270
<http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?uid=1414270&form=6&db=m&Dopt=b>

Normal cholinergic function*



*Adapted with permission from Adem A. Putative mechanisms of action of tacrine in Alzheimer's disease. *Acta Neurol Scand Suppl.* 1992;139:69-74. PMID: 1384265
<http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?uid=1384265&form=6&db=m&Dopt=b>

Therapeutic Approaches

- Glutamate neurotoxicity
- Memantine partially blocks the N-methyl-D aspartic acid (NMDA) receptor and prevents excess stimulation of the glutamate system.
- Excessive activation of the NMDA receptor by glutamate increases the vulnerability of CNS neurons leading to degeneration.

Acetylcholinesterase inhibitors (AChEIs) are the best developed therapy and are used for mild to moderate disease.

The mechanism by which AChEIs slow progression of disease is thought to be by increasing levels of ACh at the synapse and possibly affecting amyloid production.

Tacrine was the first widely used AChEI

A 30-week randomized control clinical trial showed a significant dose related improvement in cognitive function. However, subsequent studies were less impressive and a short half-life, hepatotoxicity, and cholinergic side effects have limited the use of this drug.

Second generation cholinergics,

donepezil (trade name Aricept)

galantamine (trade names Reminyl, Nivalin, Razadyne)

rivastigmine (trade name Exelon)

fewer side effects,
longer half-lives,
greater efficacy.

AChE I

- In a meta-analysis of 29 randomized placebo-controlled trials, patients on cholinesterase inhibitors improved 0.1 standard deviations (SDs) on
- activity of daily living (ADL) scales and 0.09 SDs on instrumental ADL scales compared with placebo. This effect is similar to preventing 2 months per year decline in a patient with AD.
- Typically, AChEIs are started at low doses to minimize side effects such as facial flushing, dyspepsia, nausea, vomiting, and diarrhea. The dose is then titrated up to the maximum tolerated dose

Treatment

- In all studies reviewed that examined an AChEI vs placebo, in mild to moderate AD, the ADAS-cog showed a decrease of between 2-4 points. The largest changes were with rivastigmine.
- The ADAS-cog is a validated assessment scale that measures attention, memory, orientation language and praxis in AD.
- Scores range from 0-70, with higher scores indicating greater impairment.

Treatment

- Memantine was not found to be useful in mild to moderate AD but two studies found some benefit in mild to moderate vascular dementia.
- Donepezil did not have a significant effect in MCI with the measures used.

Treatment

- In general, the results of several randomized, double blind, placebo controlled trials with at least 6 months duration, with donepezil, galantamine or rivastigmine at the recommended doses for patients with mild, moderate or severe dementia of the AD type, produced improvements in cognitive function on average of about - 2-3 points on the ADAS –cog. However, global assessment of functioning was rated more positively and there were benefits seen on ADL and behavior. (van Marum. 2008 Fundamental and Clinical Pharmacology 22:265-74).
- Memantine, in general, is less effective than the AChEIs and is only approved for moderate to severe dementia.

Treatment

- In very large meta analysis of the major studies involved in AChEIs and memantine in AD, MCI and vascular dementia (Raina et al. 2008 .Annals of Internal Medicine v 148, n 5, 379-399), using 96 papers representing 59 studies which used randomized controlled trials of the 5 agents approved by the FDA in adults with a DX of dementia:
- Both AChEIs and memantine had consistent effects on cognition and on global assessment, but the effect sizes were small.

Combined treatment

- Memantine, at 20 mg once daily, was added to stable AChEIs treatment (all three) in 433 patients with probable AD (MMSE 10-22) and the usual measures were evaluated (ADAS-cog, CIBIC-Plus, NPI and ADCS-ADL and MMSE). There was no significant advantage of the combined therapy vs monotherapy on any of the measures used. (Porsteinsson AP et al 2008
Curr.Alzheimer Res. 5:83-89)

Therapeutic approaches based on pathogenic mechanism

- NGF gene delivery
- Oxidative stress
 - Selegiline
 - Alpha-tocopherol
- Amyloid cascade
 - Statins
- Ab vaccination
- (passive and active therapies)
- Secretase effectors
- SALAs
- Inflammation
 - NSAIDs
- Excitotoxicity
 - Memantine

Immunotherapies

- Vaccines
 - AN1792—trial in 2000—was stopped due to encephalitis in a few of the patients (very small trial).
 - Six-year follow-up of eight patients from original AN1792 active immunization trial—confirmed that vaccination with full-length A β 42 can clear amyloid plaques but showed that this clearance did not slow disease progress.
 - Mean A β load was lower in the vaccinated patients (2.1 versus 5.1 percent in controls), and though the extent of plaque removal varied greatly, it did correlate to some degree with serum anti-A β antibody titers, the researchers found.

Immunotherapies

- In the small cohort they were able to analyze, the researchers saw no measurable clinical gains in the AN1792-treated group. In fact, two patients with near complete clearance of amyloid plaques still succumbed to profound end-stage dementia before they died. Overall, the immunized patients did not live longer, nor did they take longer to reach severe dementia, compared with controls.
- Passive immunization trials are under way.

Immunotherapies

Other immunization strategies (e.g., passive immunization and active immunization with truncated versions of A β) can be effective at clearing plaques but several researchers predict that these changes will not correlate well with cognitive improvement. However, newer protocols may have differential effects on the various forms of A β (e.g., plaque, soluble, oligomeric, intraneuronal), which could in turn lead to different cognitive effects. There may be cautious hope in using immunization to prevent AD rather than treat it. "A study to determine if A β immunization at a young age could prevent the development of AD later in life would be the ultimate test of the A β hypothesis."

Anti-inflammatory therapy or SALAs

Tarenflurbil (trade name Flurizan), the R-enantiomer of the non-steroidal anti-inflammatory, flurbiprofen, is an inhibitor of γ -secretase, the second of two enzymes that cleave amyloid- β (A β) from its precursor protein. The hope was that tarenflurbil would limit production of A β and slow or halt disease progression

Tarenflurbil has floundered in an 18-month Phase 3 clinical trial in patients with mild Alzheimer disease. According to a June 30 press release from one of the sponsors of the drug, the study did not achieve statistical significance on either of its primary endpoints—cognition and activities of daily living. The results have prompted the company to discontinue the drug.

Statins

- Cholesterol Hypothesis:
 - Increased levels of cholesterol promote A beta production.
 - Treating animals with statins decreased A beta
 - Retrospective studies have shown an association between statin use and decreased prevalence of AD.

Statins

- Longitudinal studies have not shown a decreased risk of AD among statin users vs non-statin users.
- Patients taking a combination of atorvastatin (trade name Lipitor) and donepezil fared no better than those taking donepezil and a placebo. Though a pilot study of atorvastatin alone suggested some benefit in AD patients other data is equivocal. Epidemiological studies suggest either no protective effect of statins for cognitive decline or an effect for just simvastatin), while several case-control studies also show no benefit.

Statins, cont.

- A pharmaco-epidemiological study looks at people with risk factors for the medicine that they are taking. Thus, if we look at statins by epidemiology, the patients all had high cholesterol (before taking the statin), which is a risk factor for AD. If you reduce that risk factor, you reduce AD. If you do the same study prospectively, as with the LEADe study, the patients do not have this cardiovascular risk factor. So perhaps in this case the statin has no benefit because there was no cholesterol-related risk factor to start with.
- LEADe is a study of patients with lower cardiac risk and lower cholesterol levels. This leaves unaddressed the question of whether atorvastatin would have an effect in the large group of people with high LDL cholesterol and high cardiac risk.

Back to the Future

- **Dimebolin hydrochloride (trade name Dimebon)—a weak inhibitor of cholinesterase and NMDA receptors with neuroprotective properties—improved mild to moderate AD patients in all five of the study's outcome measures (four cognitive, one global). What's more, dimebolin hydrochloride's benefits seemed to hold, and by some measures even increase, through the trial's six-month blinded extension. The authors note that these persistent benefits distinguish the small-molecule drug from existing approved therapies for mild to moderate AD—none of which have shown increasing improvement past 12 months.**
- Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin SO, Seely L, Hung D on behalf of Dimebon investigators. Effect of Dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Lancet 2008 July 19;372:207-215.

Dimebolin hydrochloride

- In this Russian trial, dimebolin hydrochloride was safe and well tolerated. At week 26, dry mouth and depressed mood were the most common adverse events (14 percent for each symptom, versus 5 percent of placebo patients).
- “It’s very important that the field be investigating non-amyloid-based interventions as well as amyloid-based interventions,” said Jeff Cummings of UCLA , who serves on the steering committee to help design dimebolin hydrochloride trials. **“This non-amyloidogenic pathway involving unique mechanisms of action appears to result, in this first pivotal trial, in a good effect size, a consistent effect across measurement instruments, and a more persistent effect than we have seen in previous trials.”**

Neurotrophins

- Much animal data to support the effects of NGF in protection of basal forebrain cholinergic neurons.
- However, the inability of NGF to cross the BBB, its short half life and its broad effects make clinical application difficult.
- In 2001 a human clinical trial was started with 8 early stage AD patients injected with mouse NGF into their nucleus basalis. Serial PET scans in 4 subjects demonstrated reversal of the pattern of metabolic decline seen in AD. ADAS-cog and MMSE showed reduced cognitive decline in these individuals but the study has no controls subjects and is very small.

Neurotrophins

- Phase I clinical trial of AAV (adeno associated)-NGF gene delivery in early to mid stage AD are pending
- Phase II multicenter trials with sham surgery controls are being planned.

Aggregation inhibitors

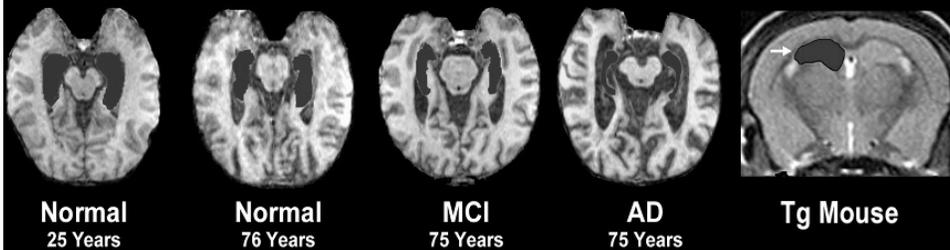
- Tramiprosate (Alzhemed) was designed to prevent amyloid deposition in the brain and this modify the course of AD.
- It is a glycosaminoglycan designed to interfere with Abeta early in the cascade of amyloidogenic events. It is a modification of the aa, taurine.
- Tested in clinical trials in US and Europe in mild to moderate AD.
- The recent US phase 3 trial is considered to have failed and the EU phase 3 trial has been discontinued.

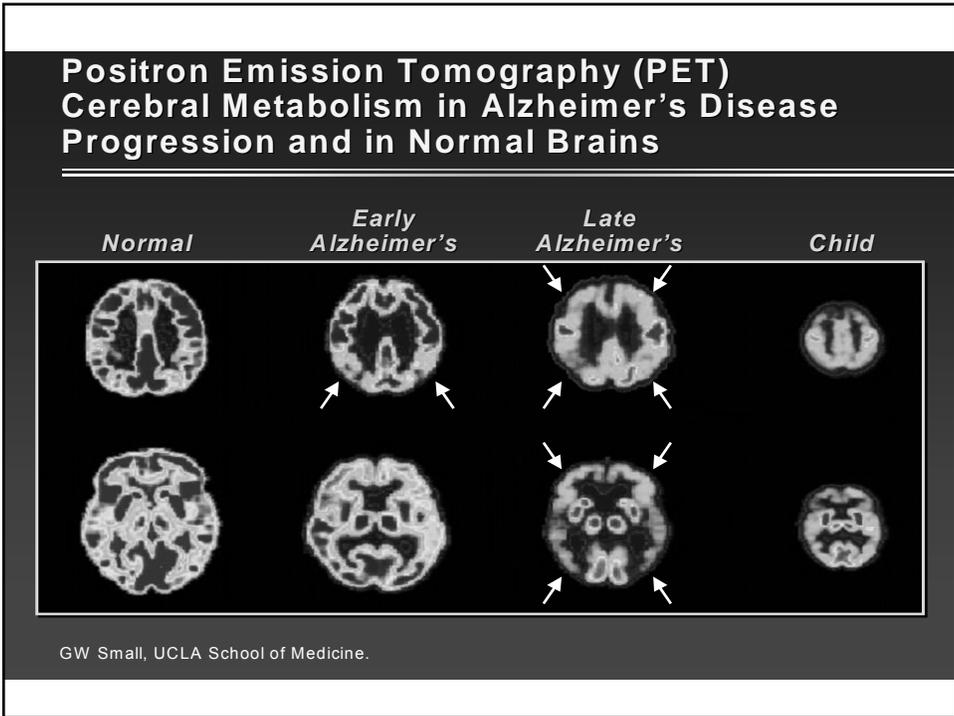
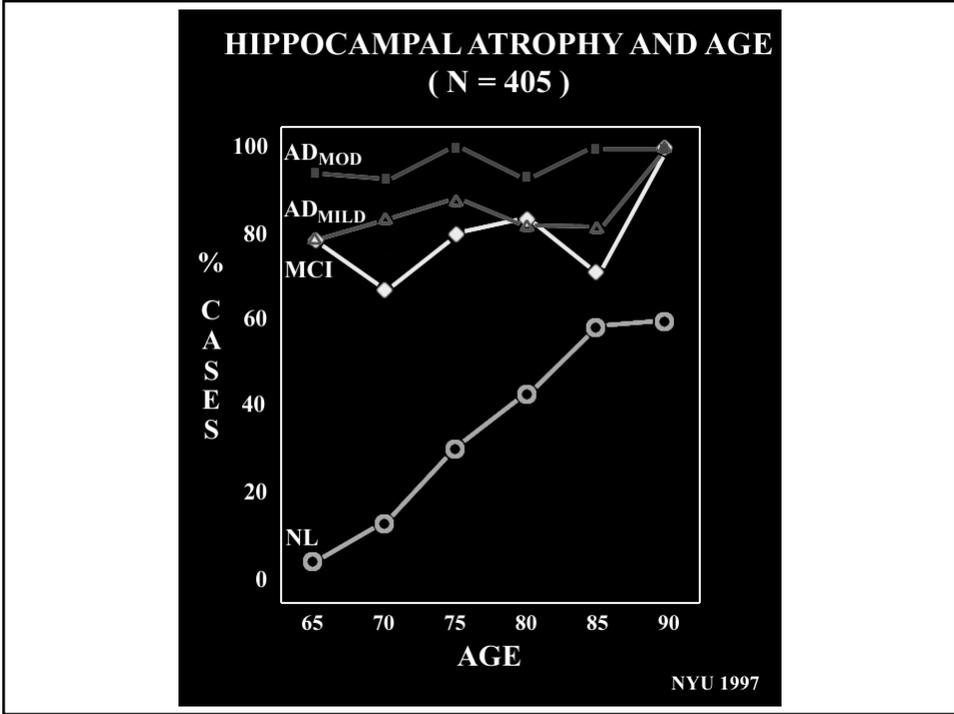
What's next?

- Better biomarkers to test new strategies
 - CSF levels of A beta or tau
 - blood proteomics
 - smaller hippocampal volumes on MRI
- Or a combination of all of the above

May think about identifying subgroups of AD patients: i.e. those with high oxidative stress markers, i.e. lipid peroxidation products like isoprostanes, may progress faster and may respond better to antioxidants.

The Anatomy of Memory Hippocampus Size in Aging and AD

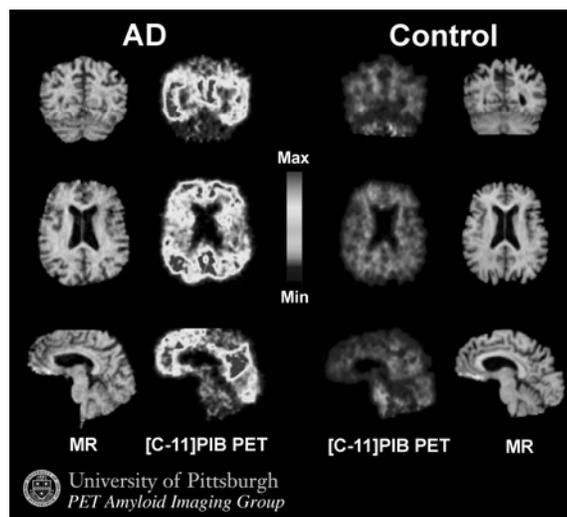




What's next?

- Better imaging compounds
 - PIB
 - PK1195
 - DTI
 - Other markers in development

The future: Amyloid Imaging



William E. Klunk, MD, PhD

Prevention

- **Exercise**

- The Burns study, which appeared in the July 15 issue of Neurology, asks whether fitness level affects brain changes seen early in AD. The researchers measured the fitness of 57 early-stage AD patients, and a similar number of non-demented subjects, during exercise on a treadmill, and determined whole brain volume by MRI. Their results indicate that subjects with AD had a modestly but significantly reduced maximum oxygen consumption (a measure of cardiorespiratory fitness) compared to non-demented subjects. Fitness level correlated with brain volume in the AD group, so that people with AD who were in better shape had more brain tissue. There was no such relationship in people without dementia, and there was no correlation between brain volume and cognitive measures after adjustment for age.

Exercise

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Prevention

- Diet
 - Mediterranean diet: high intake of fish, low to moderate intake of saturated fatty acids. low to moderate intake of dairy products and meats and moderate amount of ethanol(red wine).
 - Associated with lower AD risk
 - Associated with lower mortality in AD

Prevention

- Many studies have shown that a higher level of education is protective against Alzheimer's disease.
- A possible explanation for the finding is the theory of 'cognitive reserve'.
- This theory suggests that the brain's ability to cope with Alzheimer's disease varies from person to person, but the number of neurons and synapses are likely to be more numerous in people who are highly educated.
- Alternatively, even if the quantity of neurons and synapses is no different, the synapses are likely to be more efficient and/or the alternative circuitry is likely to be operating in those who are highly educated.
- However, one study showed that although AD started later in subjects with a higher level of education, once it did start it progressed more rapidly.

What we don't know

- Genetics
 - Several genes identified but as of yet these genetic mutations make up a small number of families with AD
 - ApoE4 is a risk factor and can be measured. Not recommended as general clinical test, as of yet.
 - More genes to come and may point the way to better strategies for intervention.

Genetic classification of the dementias: the Alzheimer's Diseases

Type	Chromosome	Gene
Early-onset familial autosomal dominant mutation, AD1	21	APP
Late-onset familial and sporadic associated susceptibility gene, AD2	19	APOE genotype
Early-onset familial autosomal dominant, AD3	14	Presenilin I (S182)
Early-onset familial autosomal dominant (Vogt-German founder and others), AD4	1	Presenilin II (E5.1, S121)
Other late-onset susceptibility genes	Several reported, but unconfirmed	

What we don't know

- Environmental Influences
 - Education – we do know
 - General health: hormonal
 - Brain insults: e.g. multiple anesthetics, head trauma
 - Stress: severe trauma in early life or long lasting trauma
 - Medications : antidepressants, valproate, etc.
 - Happiness and Purpose in Life

Issues for future studies

- Better understanding of the neuropathology of AD i.e. tau and its hyperphosphorylation
- More defined clinical subtypes of early stages of cognitive impairment (amnestic, visuospatial MCI)
- Better biomarkers (plasma Abeta and/ or tau, synaptophysin)
- Better methods to test efficacy of possible new disease-modifying strategies; i.e. longer trials (not 6 months but 18 months); better cognitive and functional end points.

A husband's poem

- As night approaches, ever slowly.
The light of reason dims and fades.
What used to be a mind that does
Is now a mind that never was.
and memories that once we knew
Will vanish as the morning dew.
- And yet, and yet
A spark remains
Though in the shade
Until it too
Will dim and fade.