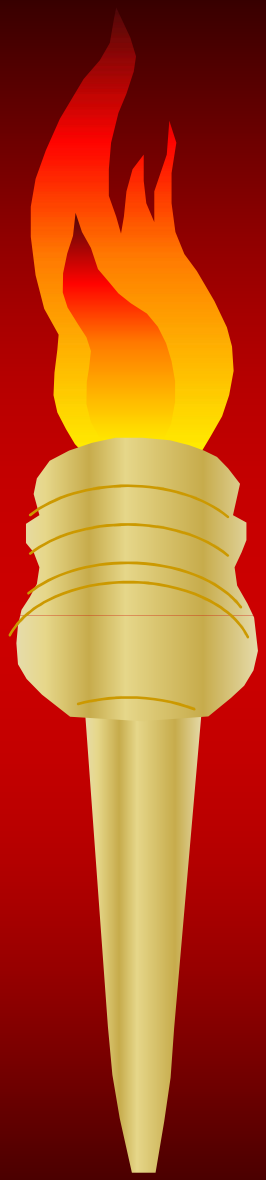
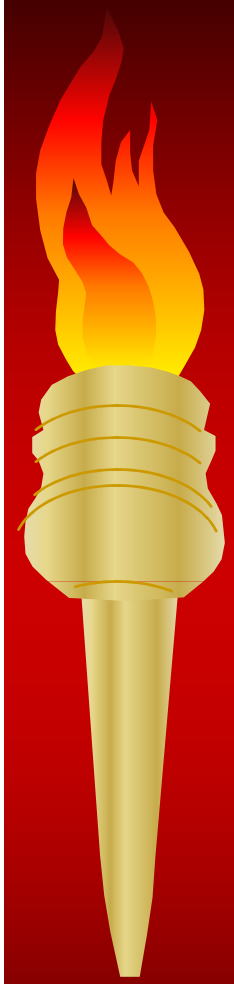


Alzheimer's Disease Education & Training Conference
February 19, 2011

Current Concepts in Dementia Research & Treatment

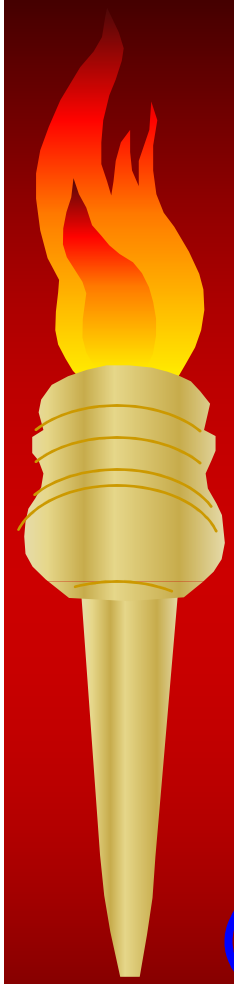
Alice Pomidor, MD
Florida State University College of Medicine

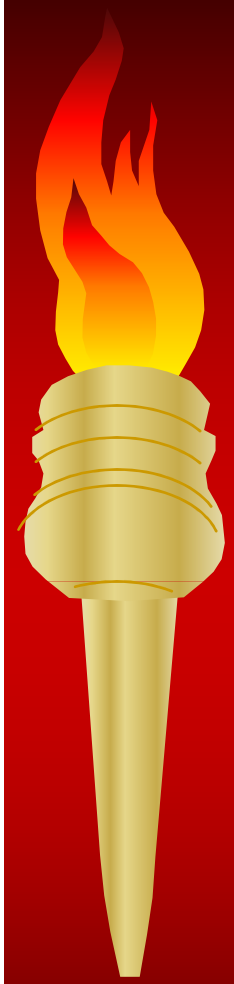


Objectives

- Briefly review theories about the causes and risk factors for Alzheimer's-type dementia (AD)
- Discuss recent research findings related to Alzheimer's
- Present currently ongoing research studies of Alzheimer's

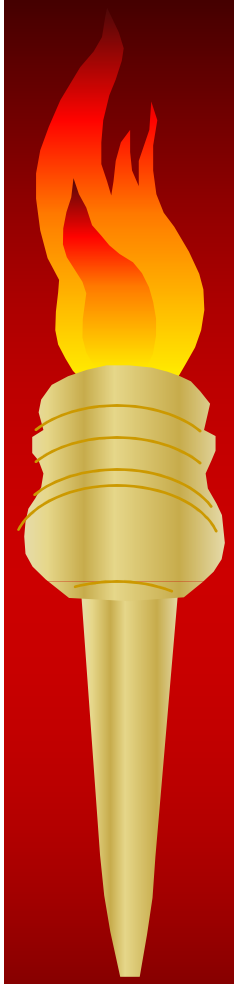
Different types of Dementia





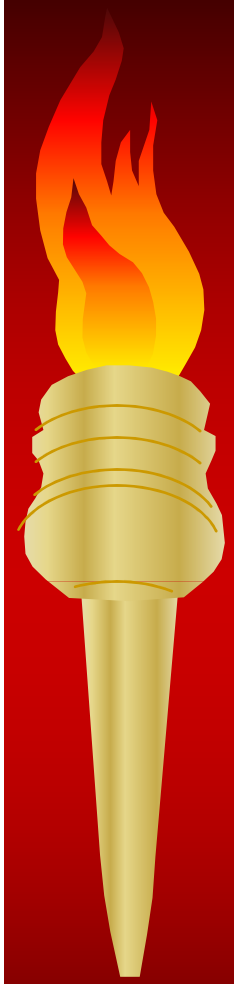
Research Areas

- Understanding the causes and risk factors for developing AD
- Diagnosing AD early, before too much damage has occurred
- Finding ways to delay the onset, slow down, or stop the progression of dementia
- Treating the effects of dementia medically and with effective caregiving



Alzheimer's Disease (AD)

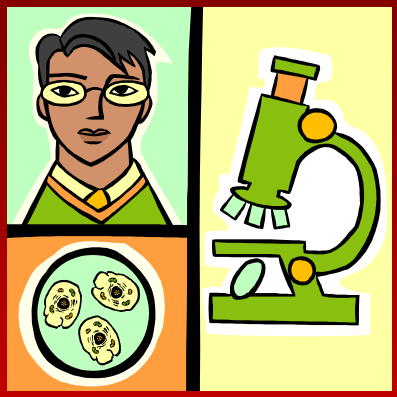
- Causes ongoing brain cell damage which leads to symptoms of:
  - Memory loss
  - Neurologic changes:
    - Language problems
    - Dressing, driving or toileting problems
    - Using objects incorrectly
    - Personality changes
  - Difficulty thinking - judgment, insight, abstract reasoning
  - Affects social functioning



A Word of Caution about **M**ild **C**ognitive **I**mpairment (MCI)

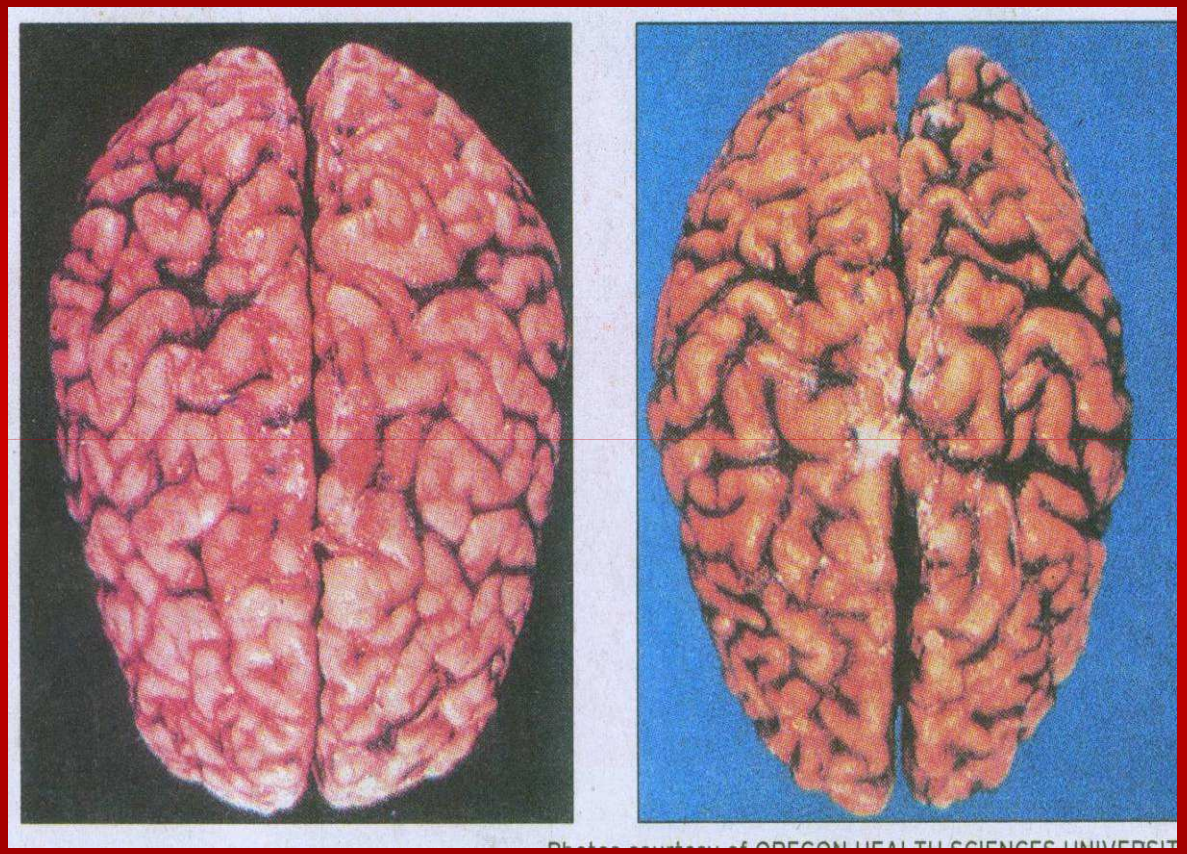
- Refers to early loss of brain function before meeting criteria for the diagnosis of dementia
- Definition varies depending on what function has been lost
- Most commonly used to refer to loss of memory only
- Beware of sweeping statements regarding the meaning, prognosis or treatment of MCI unless very clearly defined

Basic Biology of AD



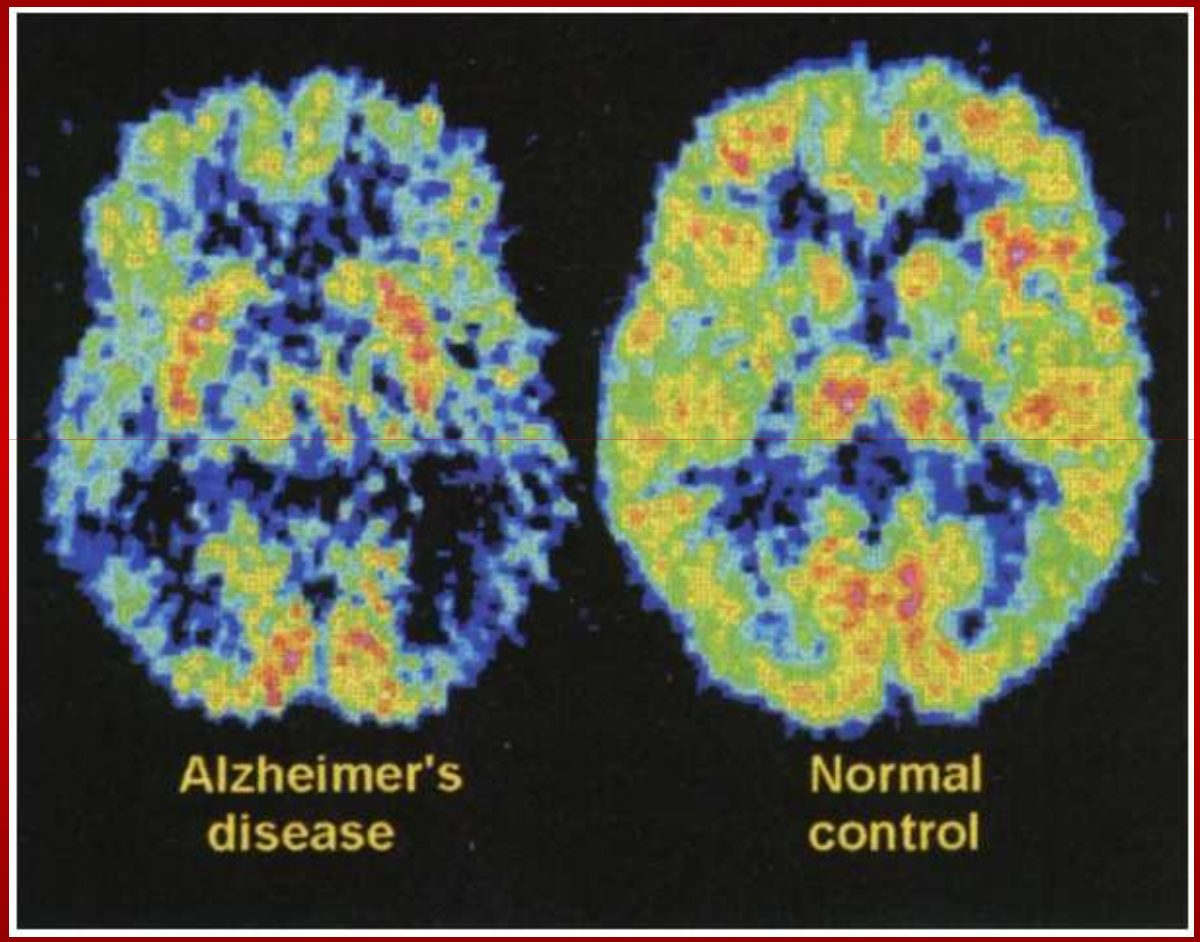
- Has 3 key features:
  - Amyloid protein **plaques** (toxic substance outside the cell)
  - Neurofibrillary **tangles** (abnormal machinery inside the cell)
  - Loss of brain cell connections and communication, causing more **cell death**

Alzheimer's Disease (AD)

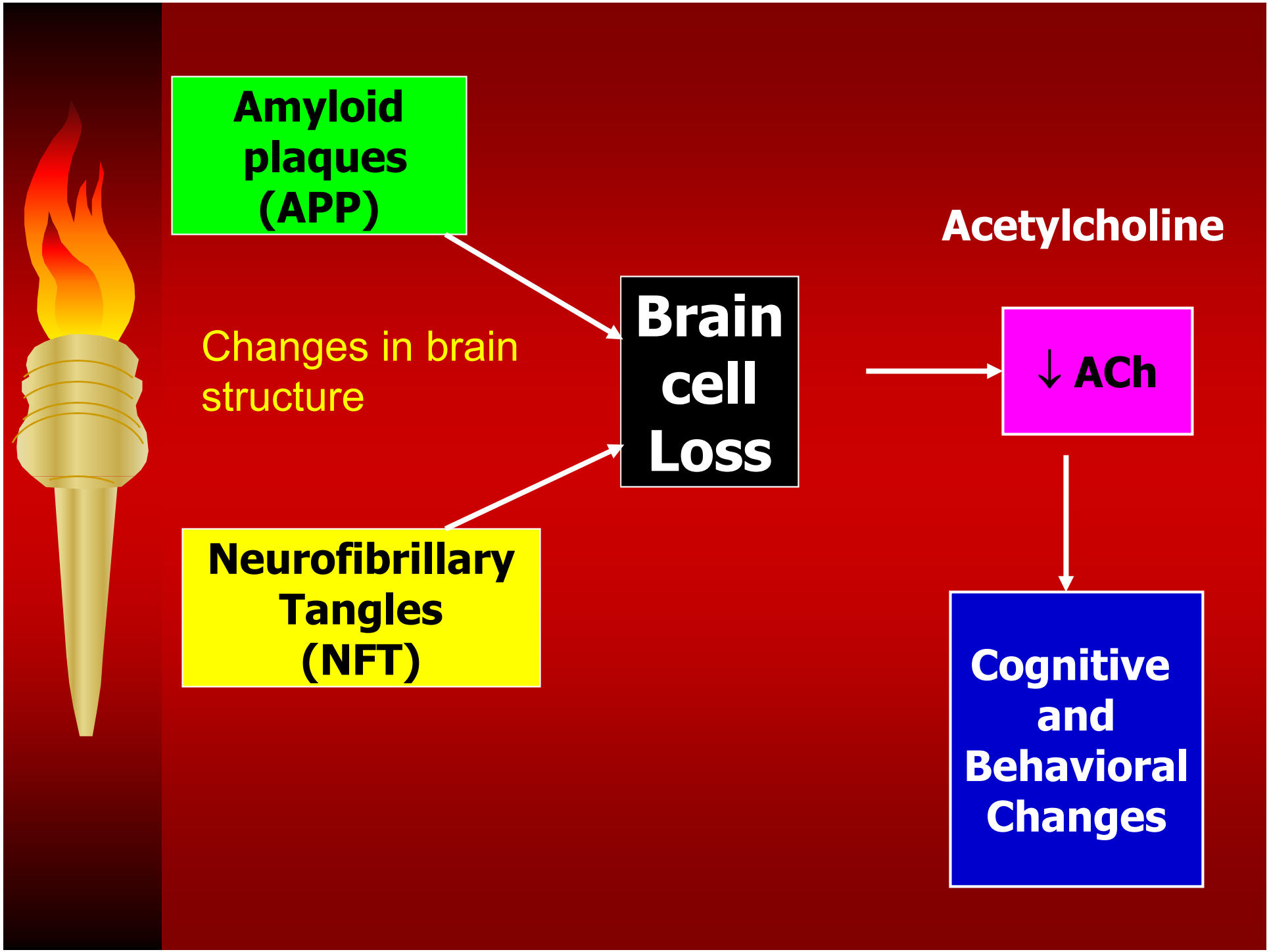


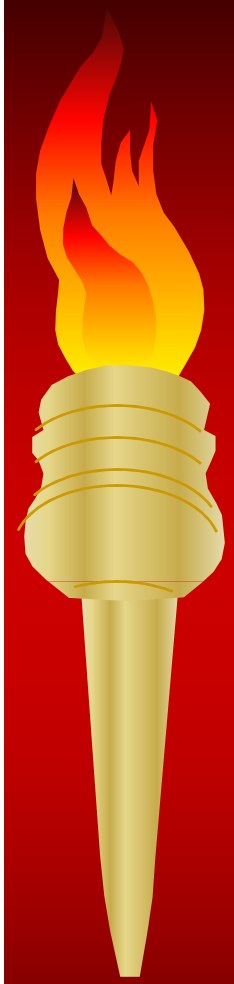
Brain shrinks as the cells die

PET Scan and AD



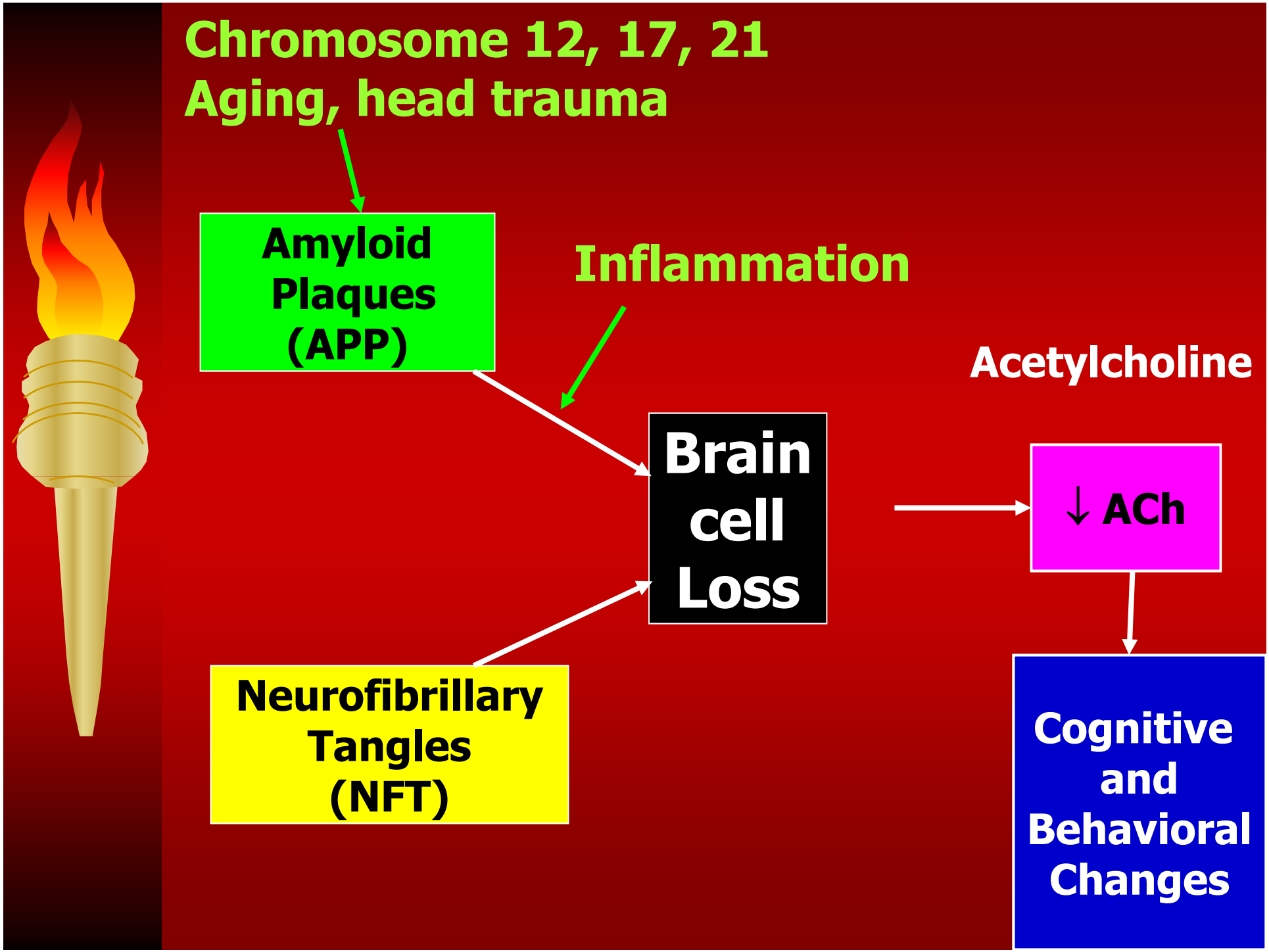
Brain can no longer work properly

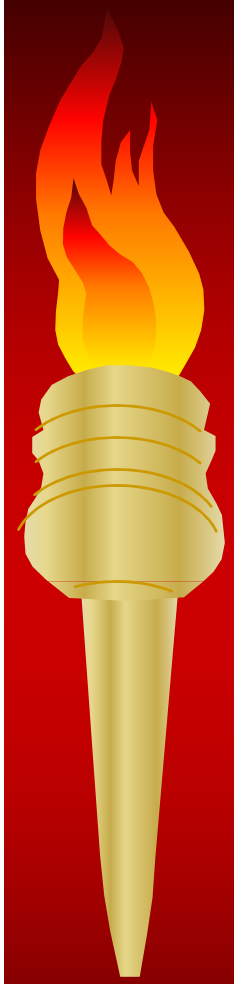

Amyloid plaques (APP)
Changes in brain structure
Neurofibrillary Tangles (NFT)
Brain cell Loss
Acetylcholine
↓ ACh
Cognitive and Behavioral Changes



Plaque-related Causes

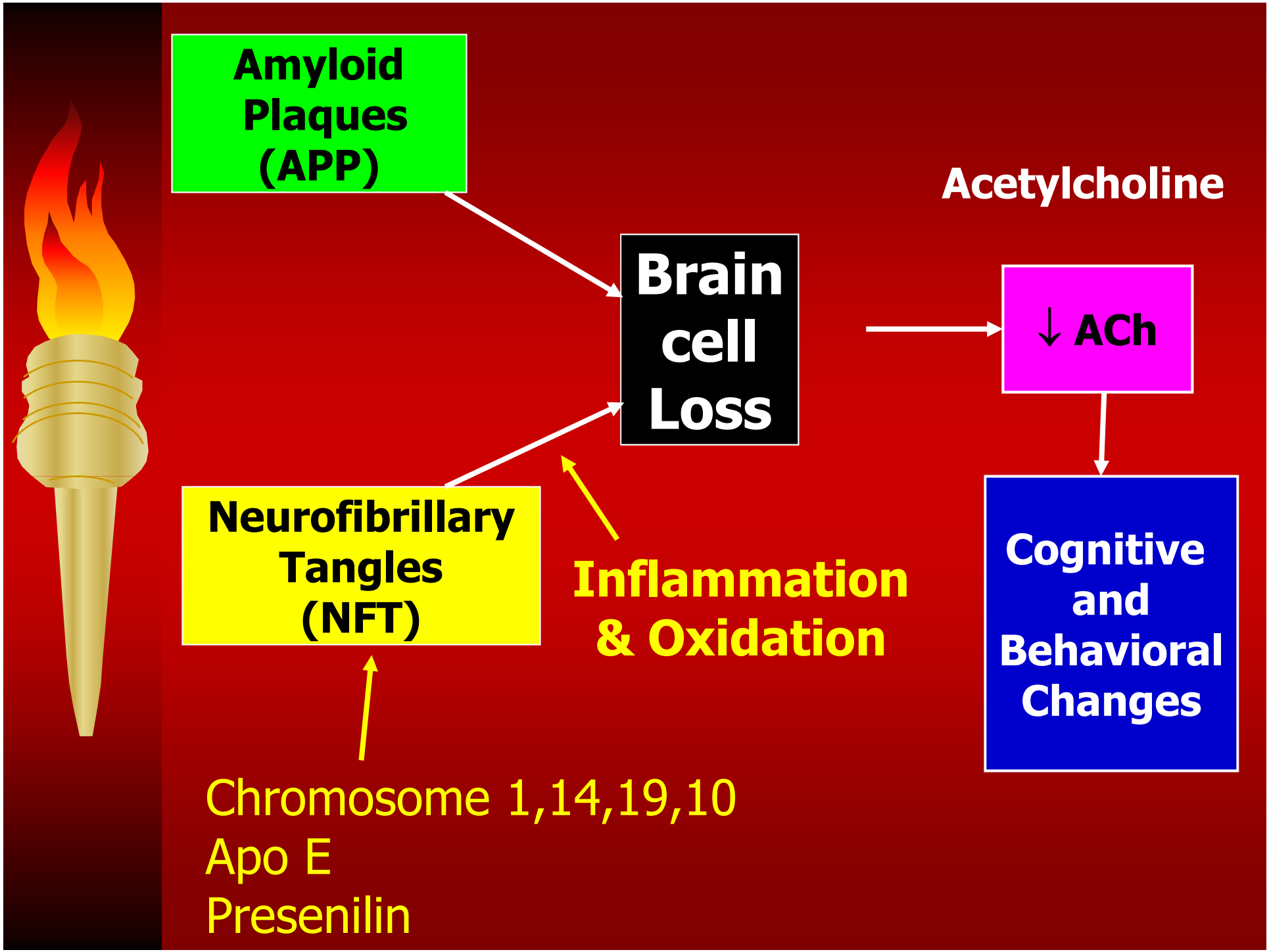
- Genetic predisposition (chromosomes 12, 17, 21)
- Difficulty cleaning up toxic proteins outside the brain cell (low cognitive reserves, aging)
- Increased burden of cell death, such as head trauma

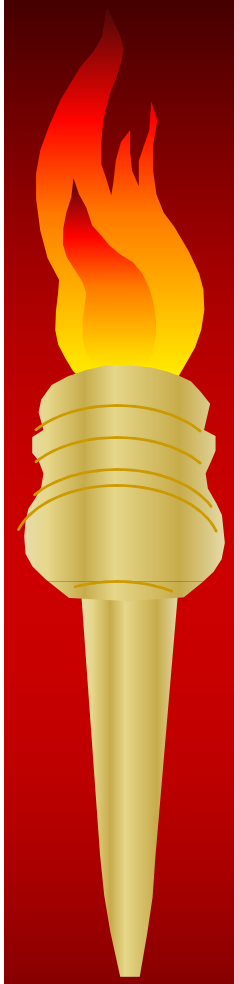

Chromosome 12, 17, 21
Aging, head trauma
Amyloid Plaques (APP)
Inflammation
Acetylcholine
Brain cell Loss
↓ ACh
Neurofibrillary Tangles (NFT)
Cognitive and Behavioral Changes



Tangle-related Causes

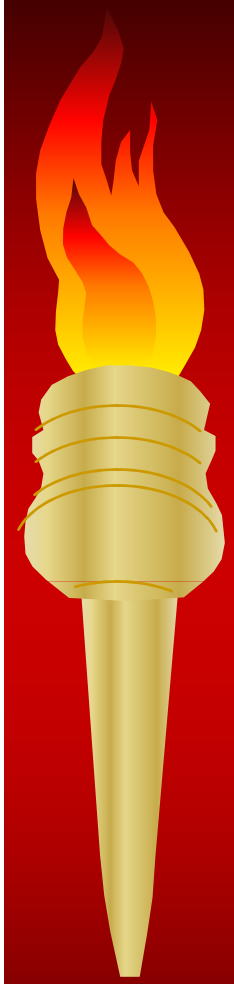
- Genetic predisposition (chromosomes 1,14,19,10)
- Fat protein changes (apolipoprotein E, cholesterol metabolism)
- Difficulty cleaning up toxic proteins inside the brain cell
- Difficulty supplying energy to the cell connections (free radicals, super oxide dismutase = SOD)


Amyloid Plaques (APP)
Acetylcholine
Brain cell Loss
↓ ACh
Cognitive and Behavioral Changes
Neurofibrillary Tangles (NFT)
Inflammation & Oxidation
Chromosome 1,14,19,10
Apo E
Presenilin



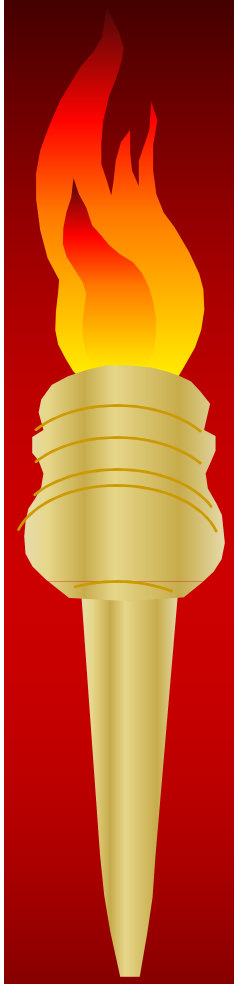
Brain Cell Additional Problems

- Brain cell (neuron):
  - Unable to talk to other cells because reception is blocked, so it dies
  - Unable to make chemicals the brain uses to communicate (called neurotransmitters) such as Acetylcholine, so show symptoms



Summary of Causes of AD

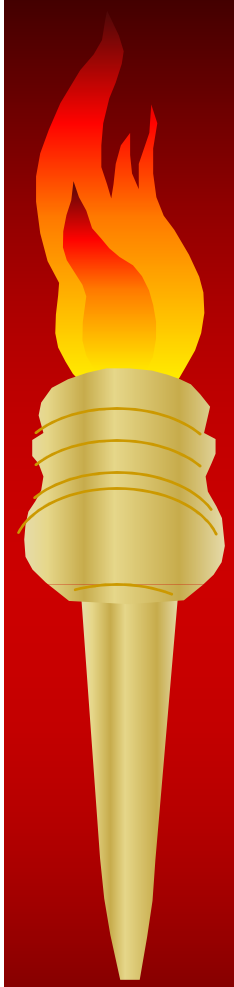
- Family inheritance of a genetic tendency to develop AD
- Making too much toxic material inside and/or outside brain cells, and/or unable to clean it up
- Problems making energy and getting it to the connections from one cell to another
- Blocked reception of brain signals
- Problems making brain chemicals



If there are so many causes, is it really one disease?

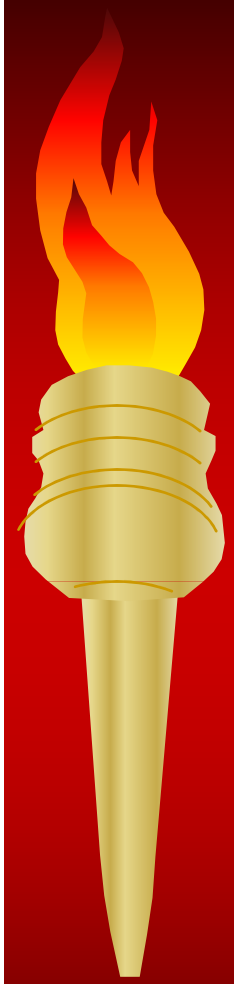
- Probably not—most likely a combination of many related factors
- May partly explain why different people behave differently
- AD persons tend to share a common pattern of behavior as time goes on
- Gives us many different opportunities to try to fix the problem

So what can Research do?



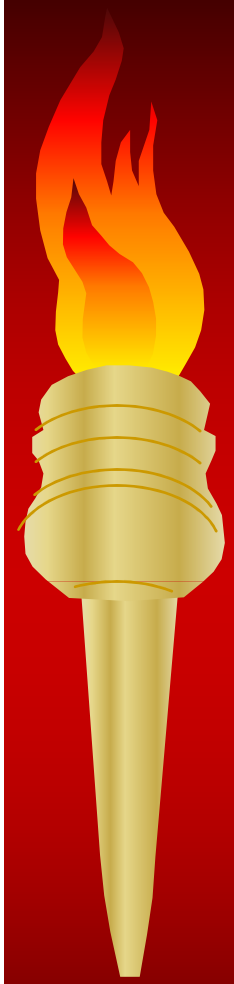
Family/Genetic Research

- Registries of families with early and late-onset disease and their unaffected family members for ongoing lab study & DNA sequencing *(Genetics Initiative)*
- Research with families who have known kinds of problems to develop interventions (ApoE)
- Gene therapy far in the future
- Protein therapies not quite as far away
- Ethics of genetic screening?
- Overlap with vascular diseases, ApoE4 gene



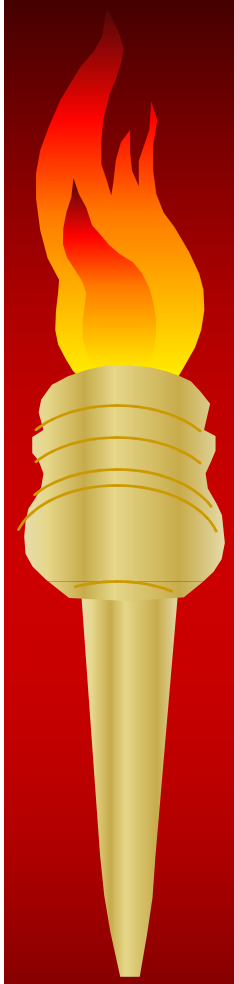
Protein Therapy

- CERE-110 uses a virus to transfer a gene that makes Nerve Growth Factor (NGF), a protein that may make nerve cells in the brain healthier and protect them from dying
- Half of the 50 patients will have CERE-110 injected into the brain during a surgical procedure, while the other half will undergo a "placebo" surgery where no medication will be injected.



Risk Factor/Lifestyle Intervention

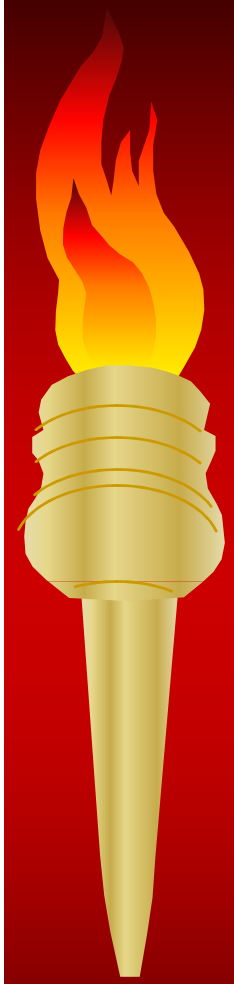
- Persons with lower educational levels and lower social interaction have higher rates of AD *(Verghese 2003, Lee 2003)*
- Education thought to build "cognitive reserve" with more connections between brain cells
- Begin early to:
  - continue in higher education,
  - participate in educational enrichment,
  - do active "brain games,"
  - engage in regular social activities



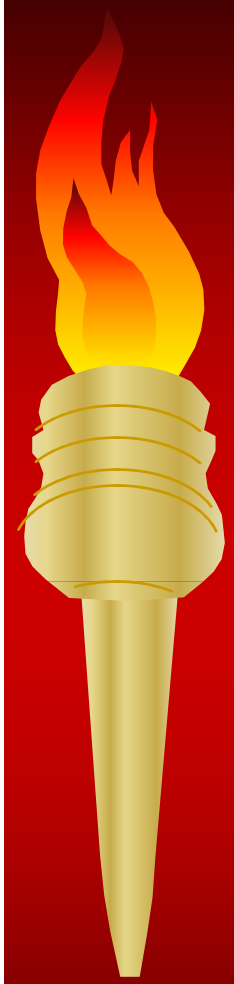
Exercise and brain function

- Brisk walkers for 6 months had increased brain function compared to physically inactive persons on MRI & intellectual testing *(Colcombe 2004)* but no data of effect on AD
- 3 trials currently ongoing to study types of activity and the effect on memory and prevention of dementia

Seniors Health and Activity Research Program-Pilot (SHARP-P)

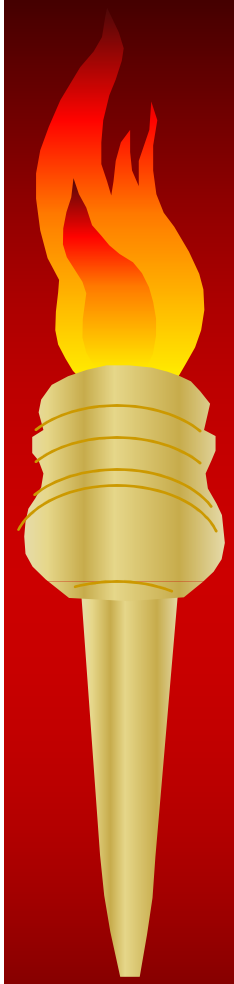


- Assess whether physical activity and cognitive training separately improve cognitive function over 6 months
- Physical Activity Training (PAT) will consist of center-based and home-based sessions to include aerobic, strength, flexibility, and balance training
- Cognitive Training (CT) to improve consciously-controlled memory and produces changes that transfer to thinking activities, memory and speed



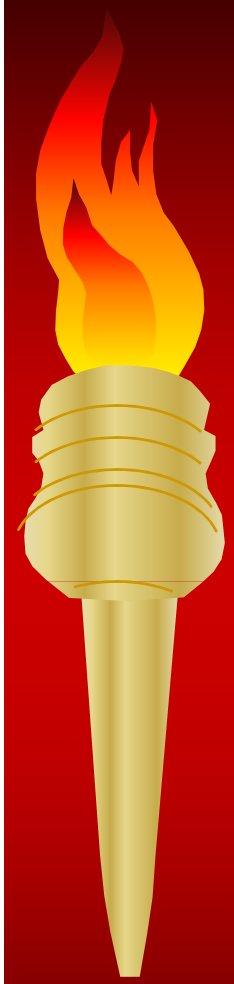
Mediterranean Diet

- 28 percent lower risk of developing MCI
- 48 percent lower risk of progressing from MCI to AD
- Includes vegetables, legumes, fruits, cereals, fish, monounsaturated fats such as olive oil, mild to moderate amounts of alcohol, and low intake of saturated fats, dairy products, meat, and poultry *(Scarmeas et al., 2009a)*.



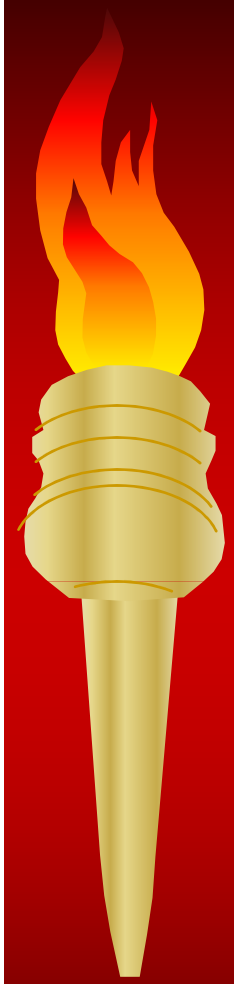
Basic Research

- NSAIDs (anti-inflammatory drugs such as ibuprofen, Celebrex)-not proven to help people in later stages as hoped but might help prevention in people with ApoE4 gene *(Imbimbo BP, Solfrizzi V, Panza F. Front Aging Neurosci. 2010)*
- Studies stopped for safety reasons due to adverse side effects of medications



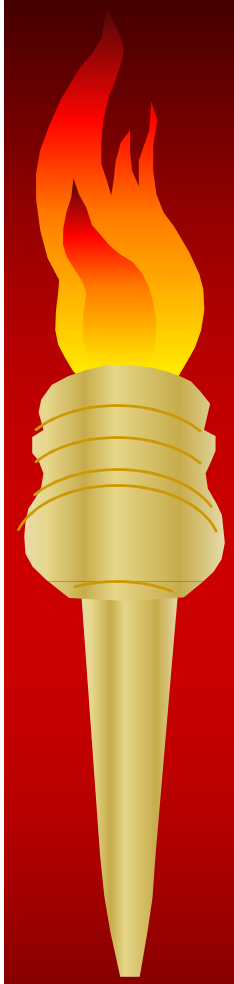
Antioxidants

- Vitamin E supplements in healthy men over age 60 still going on one more year *(PREADVISE trial)*
- Combinations trial using Vitamin E 800 IU, Vitamin C 200 mg, and alpha-lipoic acid 600 mg, CoQ 400 mg showed no firm benefit
- Resveratrol—basic actions being studied in mice for possible benefit but how it works in humans, dosage, safety guidelines not established. Study in progress.



Diabetes, Vascular Disease and Dementia

- Diabetes-Significantly increased risk of developing dementia, unclear relationships between vascular disease and what is known as AD but co-exist much of the time
- Pioglitazone & metformin-Two new studies in humans to see if increasing insulin sensitivity & decreasing inflammation in persons with early memory loss and/or metabolic syndrome will slow loss of cognitive function

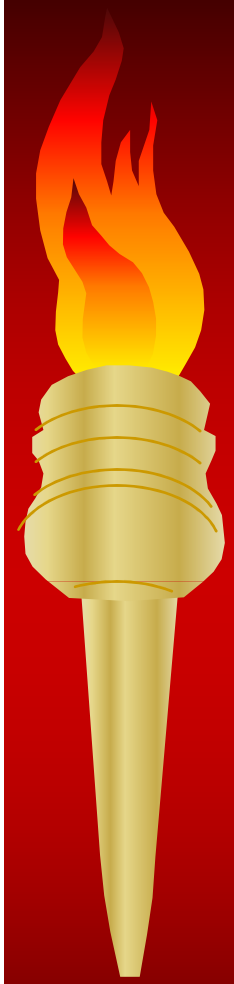


Cholesterol and Statin Therapy

- Class of medications used to lower cholesterol
- Two studies testing statins for heart disease showed less AD in those treated
- One large trial still has not released data
- Large analysis of multiple studies shows insufficient evidence to recommend treatment until last trial releases its data

McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD007514. DOI: 10.1002/14651858.CD007514.pub2

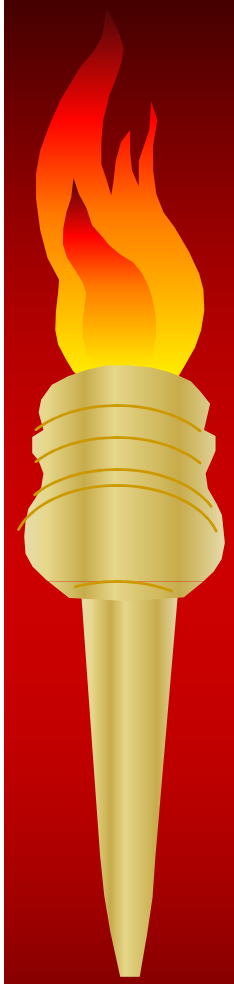
PICKLES by Brian Crane



Passive Vaccination

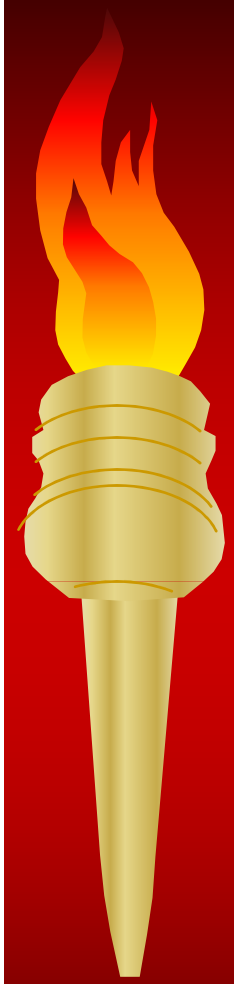
- GAP Study-ongoing, designed for mild to moderate AD patients to test the safety of a new vaccine.
- Patients receive an antibody protein which clears beta amyloid and eliminates the need for the patient to make their own. In animal studies, this clears beta amyloid from the brain just as well as traditional active immunization.

MorganD. (Alzheimer's Institute,University of South Florida, Tampa, FL, USA) Immunotherapy for Alzheimer's Disease. J Intern Med 2011;269: 54–63.



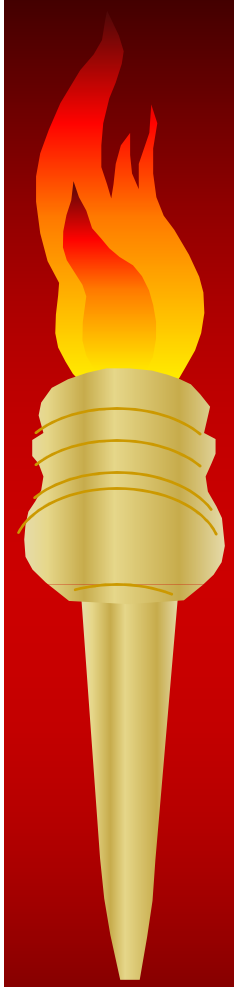
Huperzine A

- Chinese herbal derivative with chemical actions on acetylcholine similar to prescription medications
- Also reported to have antioxidant properties
- Still analyzing data as to whether is preventive or reduces severity



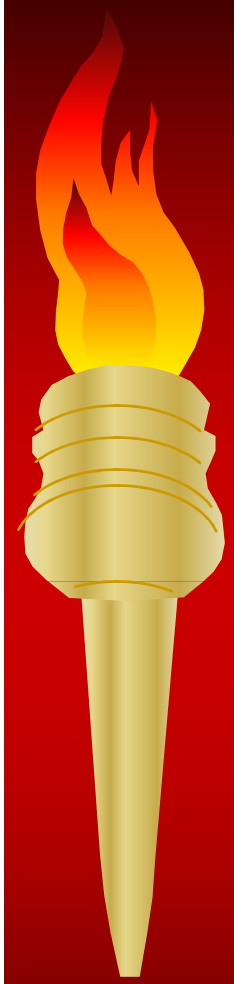
Alternative Therapy studies

- Curcumin-found in the spice turmeric, being studied for its reported antioxidant, NSAID, and cholesterol-lowering properties
- Sage-a spice with chemical actions on acetylcholine similar to prescription medications being studied to determine its effect on the cognitive function of patients with mild AD



Conclusions

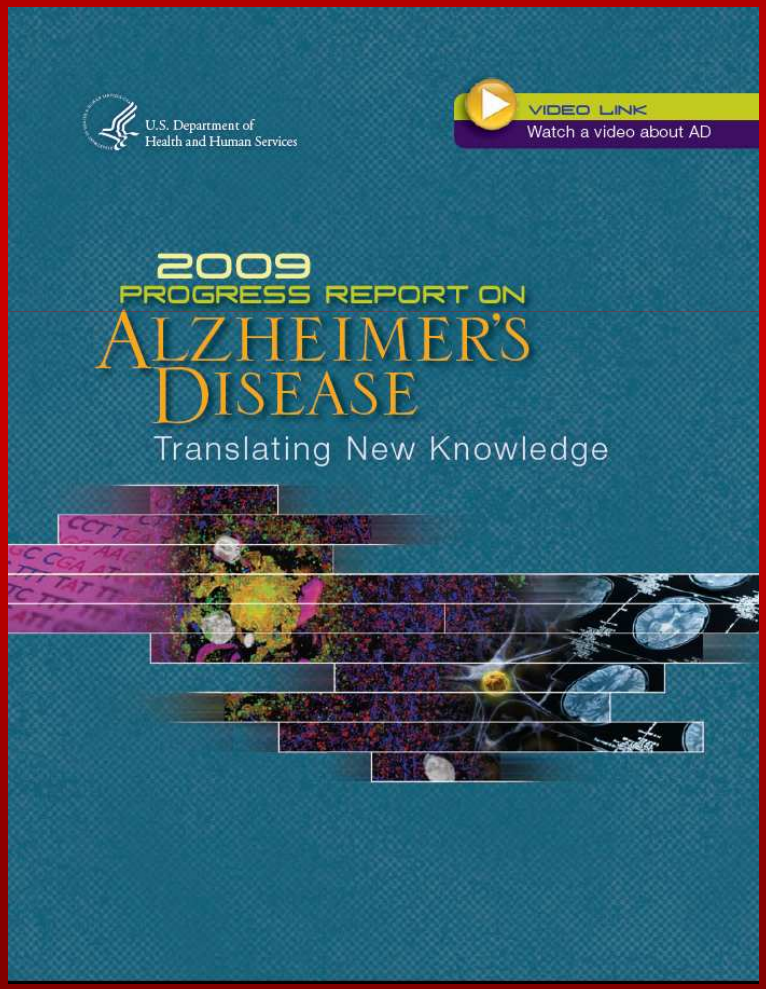
- Most hopeful avenues for therapy in near future probably those related to glucose and cholesterol management.
- Long-term, the new protein therapies being developed to stop or clear formation of toxic amyloid products in the brain most promising.
- In the meantime, effective caregiving strategies the most important for care of the Alzheimer's patient

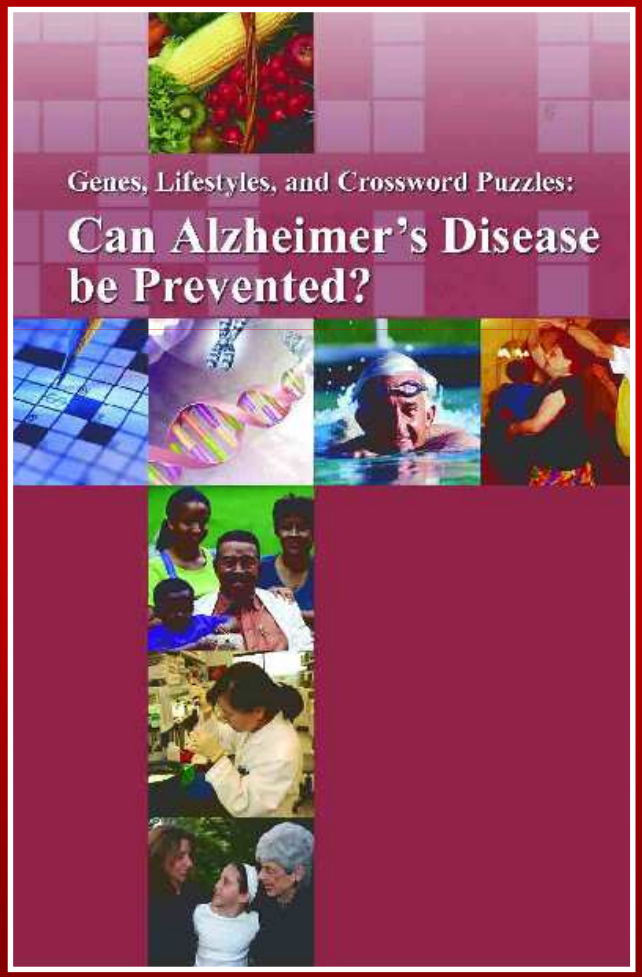


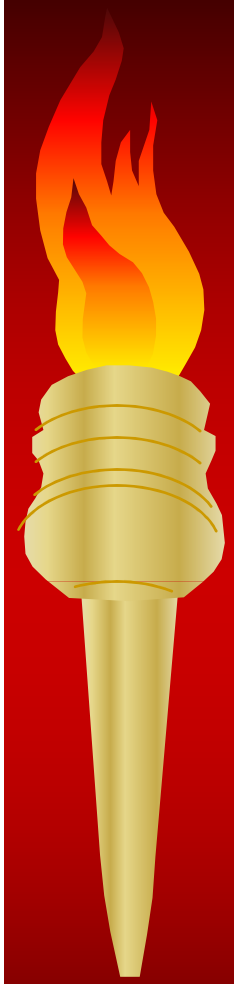
Further Conclusions

- Research for medications directed at symptom management continuing, but always side-effect issues.
- Research about measuring normal and abnormal brain function is critical to detecting early memory loss and measuring the effectiveness of treatment efforts.

National Institute on Aging







Further Information

- Alzheimer's Disease Education and Referral Center, 1-800-438-4380, http://www.nia.nih.gov/alzheimers
- Alzheimer's Foundation of America, 1-866-232-8484, www.alzfdn.org
- Alzheimer's Association, 1-800-272-9300, *Inside the Brain: An Interactive Tour*, http://www.alz.org/alzheimers_disease_4719.asp