Current Research in Other Diseases – Possible Benefits

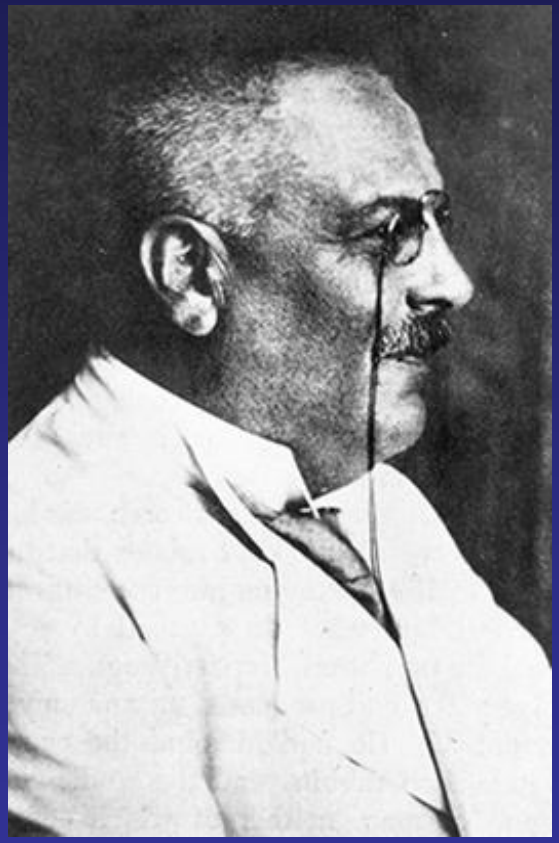
Diseases with cross-over potential

- Alzheimer disease
- Autoimmune diseases – myasthenia gravis, RA, lupus
- Duchenne muscular dystrophy

- My focus: IBM

Alzheimer Disease

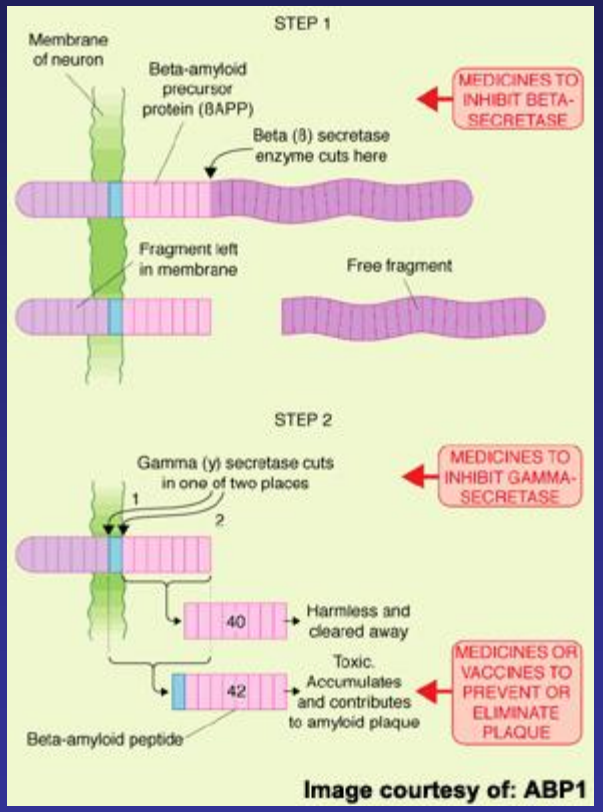
- 1st described – 1906
- Most common cause of dementia in those over 65
- Pathology includes deposition of amyloid plaques in brain



- Alois Alzheimer

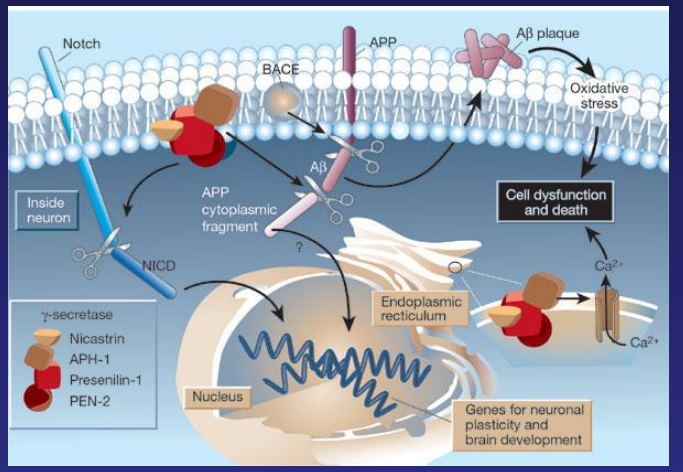
Alzheimer pathology

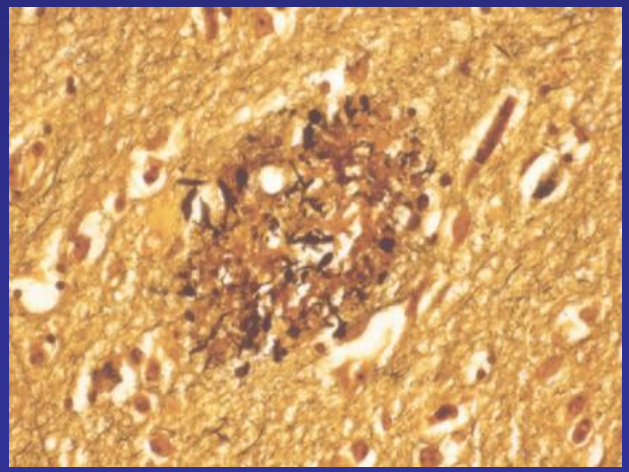
- Amyloid precursor protein (APP) is cleaved by 2 proteins, beta- and gamma-secretase



Alzheimer pathology

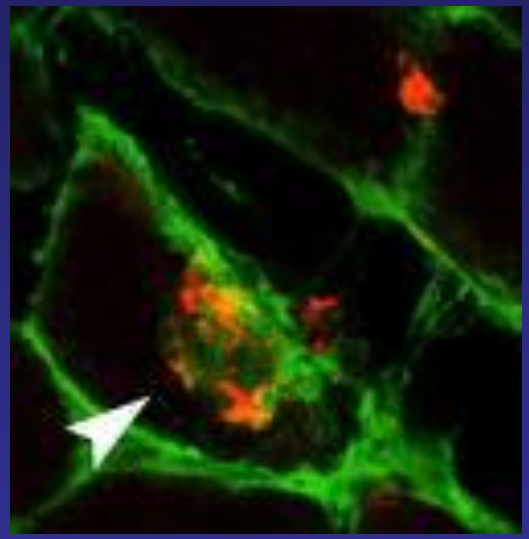
- Cleavage of APP results in abnormal amyloid deposits in brain tissue





Amyloid in IBM muscle

- Amyloid deposits also seen in IBM muscle
- Possibly, amyloid deposition leads to inflammation in the muscle
- Role of inflammation in disease progression unclear



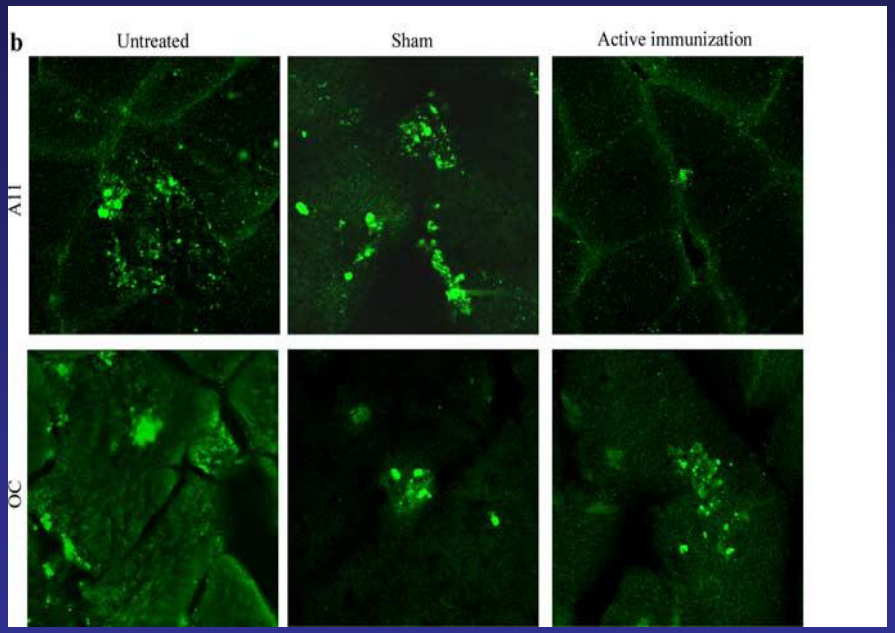
Strategies to remove amyloid

Mouse Models of AD

- Stop formation – requires identification of the primary etiology
- Slow the breakdown of APP – some progress
- Remove amyloid deposits – problems with blood-brain barrier.
- Reduce inflammation
- Possible immunotherapy

Immunotherapy for IBM

- Mouse model for IBM
- Mice immunized with a protein derived from A-beta1-33 (a fragment of APP)
- After 3 mo immunization, mice had improved rotorod performance.
- Muscle bx showed less A-beta, less vacuoles & expressed fewer stress-related proteins



Kitazawa, et.al. *J Neurosci* 2009;29:6132-6141

Lessons from Autoimmune Diseases

- Triggers for autoimmunity unknown
- Most involve a cascade of immune responses that lead to inflammation
- Most successful treatments to date directed at immune suppression
  - Side effects
- More targeted attack on the inflammatory response may be more efficacious
- Does reduction in inflammation in IBM have efficacy?

Immune therapy in IBM

- Corticosteroids
  - Reduce inflammatory infiltrates in muscle, but no increase in strength
- IVIG
  - Limited efficacy in small numbers of patients
- Other immune suppressants
  - Only anecdotal reports of disease stabilization, no clear evidence for improvement in strength
- More directed immune therapy?
  - Etanercept, et.al. – anti-TNF-alpha therapy
  - May act by reducing inflammation related to amyloid deposits in muscle