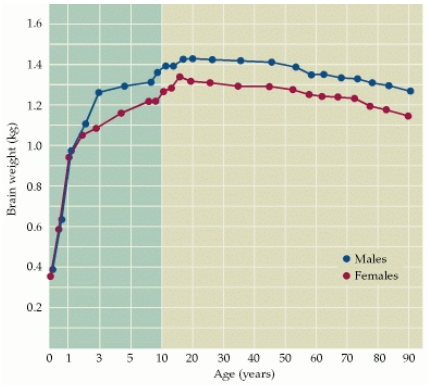
Decline in Brain Size



Brain size as a function of age. The human brain reaches its maximum size (measured by weight in this case) in early adult life and decreases progressively thereafter. This decrease presumably represents the gradual loss of neural circuitry in the aging brain, which presumably underlies the progressively diminished memory function in older individuals. (After Dekaban and Sadowsky, 1978.)

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A2220

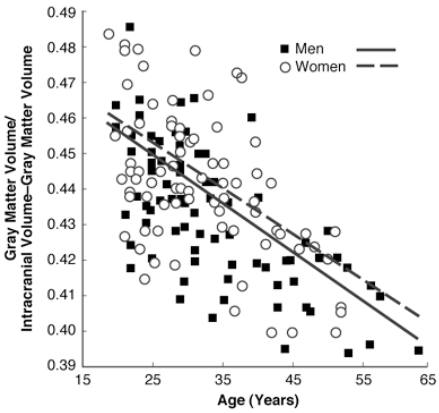
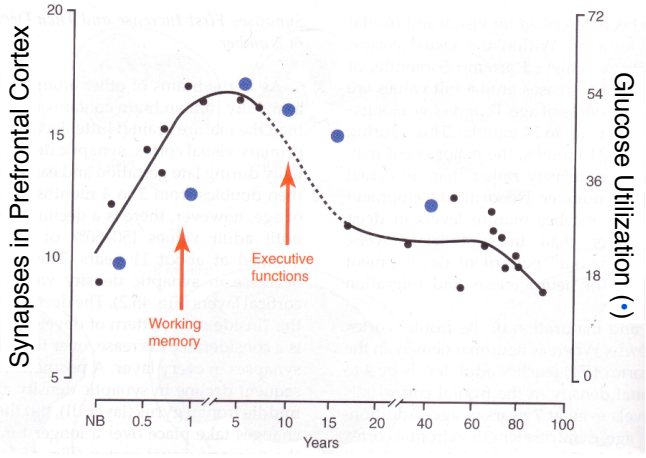


Figure 3 The proportion of intracranial volume occupied by gray matter decreases as healthy nonalcoholic men and women age, but, at any age, women have proportionally more gray matter than men.

SOURCE: Subset of the data (nonalcoholics only) reported in Hommer et al. 2001.

http://pubs.niaaa.nih.gov/publications/arh27-2/181-185.htm

Decline in Number of Synapes



Dementia

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), is a syndrome that may be caused or characterized by:

- Multiple cognitive deficits, which include:
  - memory impairment, and at least one of the following:
    - aphasia
    - apraxia
    - agnosia
    - disturbance in executive functioning.
- Social or occupational function is also impaired.
- A diagnosis of dementia should not be made during the course of a delirium.

(A dementia and a delirium may both be diagnosed if the dementia is present at times when the delirium is not present.)

multiple cortical regions dying

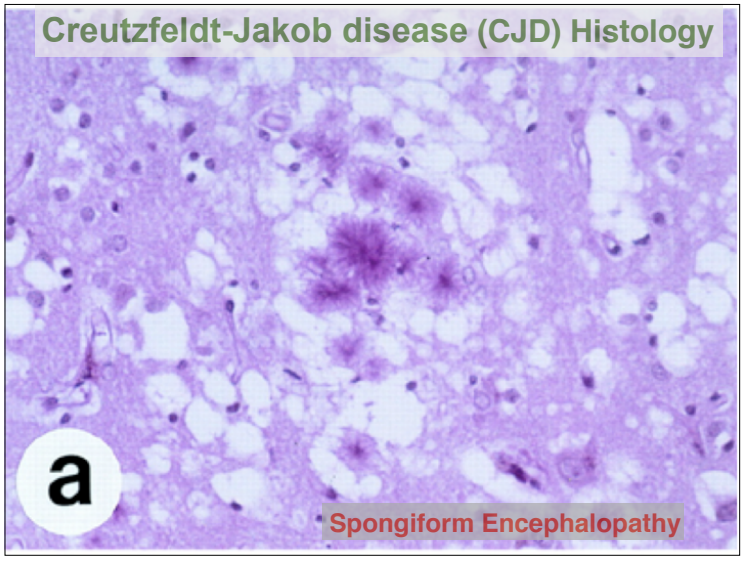
Progressive Dementias

dementias that get worse with time

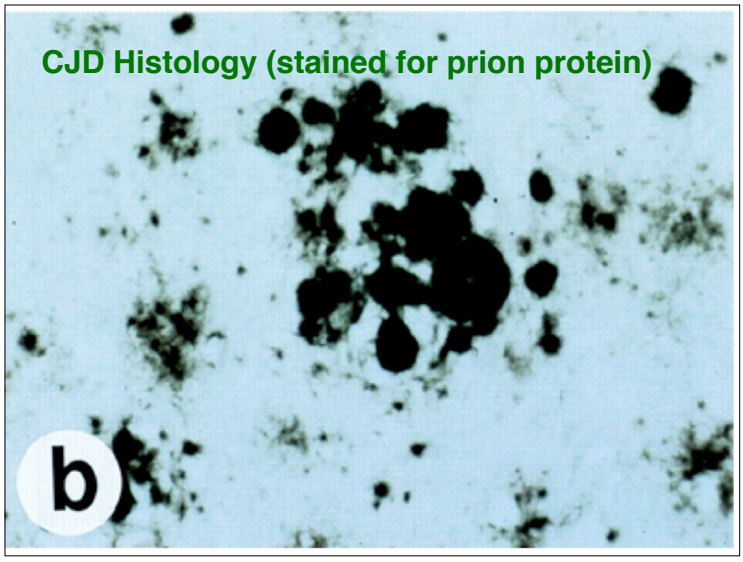
- **Alzheimer's disease.** most common cause of dementia in people age 65 and older.
- **Vascular dementia.** This dementia is a result of damage to the brain caused by problems with the blood supply to brain after stroke, high blood pressure, heart atacks or heart infections.
- **Dementia pugilistica.** aka chronic traumatic encephalopathy or boxer's dementia. Caused by repetitive head trauma, Depending on the part of the brain injured, it can cause dementia signs and symptoms such as memory problems, poor coordination and impaired speech, as well as tremors, slow movement and muscle stiffness (parkinsonism).
- **HIV-associated dementia.** Infection with the human immunodeficiency virus (HIV), which causes AIDS, leads to widespread destruction of brain matter and results in impaired memory, apathy, social withdrawal and difficulty concentrating.
- **Creutzfeldt-Jakob disease. aka Mad Cow Disease**

http://www.mayoclinic.com/health/dementia/DS01131/DSECTION=causes

Creutzfeldt-Jakob disease (CJD) Histology



CJD Histology (stained for prion protein)



Genetic Forms of CJD

sCJD – spontaneous CJD. sporadic misexpression of a protein, or mutation just in one individuals neurons

fCJD – familial CJD. spontaneous germ line mutation, so inherited and found in families
e.g. Libyan Jews; 20 different mutations found that cause fCJD

Transmittable forms (TSE)

called "**slow virus**" because long incubation time and disease showed no signs of immuno response

kuru – infection through cannibalism in New Guinea

scrapie – infection in genetically susceptible sheep (and other animals, eg. hamster)

vCJD – new variant CJD found in Britain

Prion Concept:

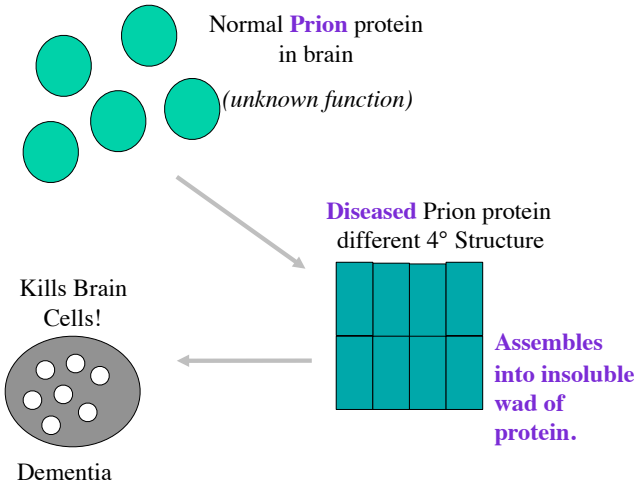
Prion - proteinaceous infectious agent w/o nucleic acid (virus and bacteria have both protein and DNA/RNA)

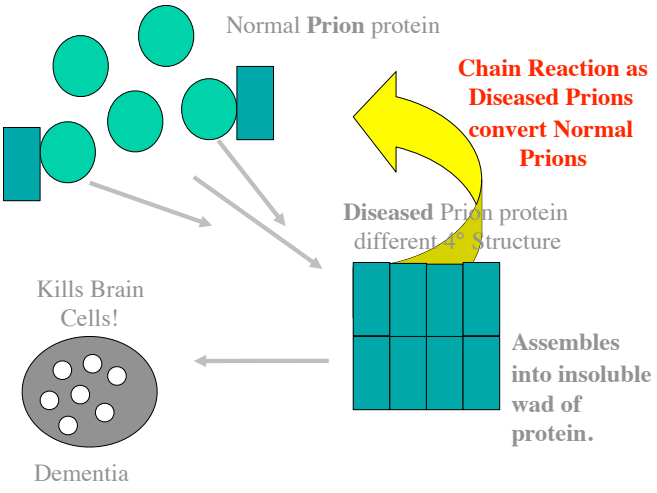
PrPc (cellular prion protein) – normally expressed throughout the brain.

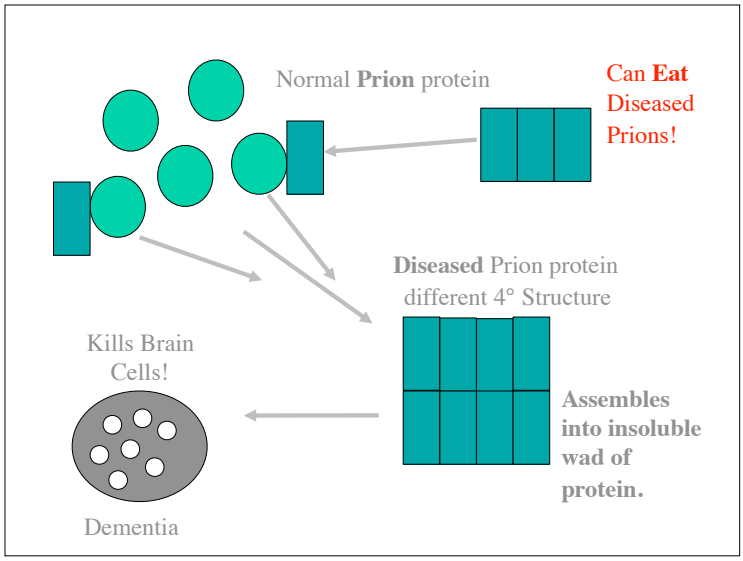
PrPsc (scrapie protein) has same amino acid sequence, but can undergo a conformational change that induces aggregation -> inclusions and apoptosis -> neuron death. (PrPsc not found in other neurodegenerative diseases)

PrPc is converted to PrPsc by PrPsc form (with help from other endogenous factors), leading to a chain reaction

PrPsc form can arise spontaneously from a misfolded PrP protein, or by mutation (and some mutations increase chances of misfolding.)



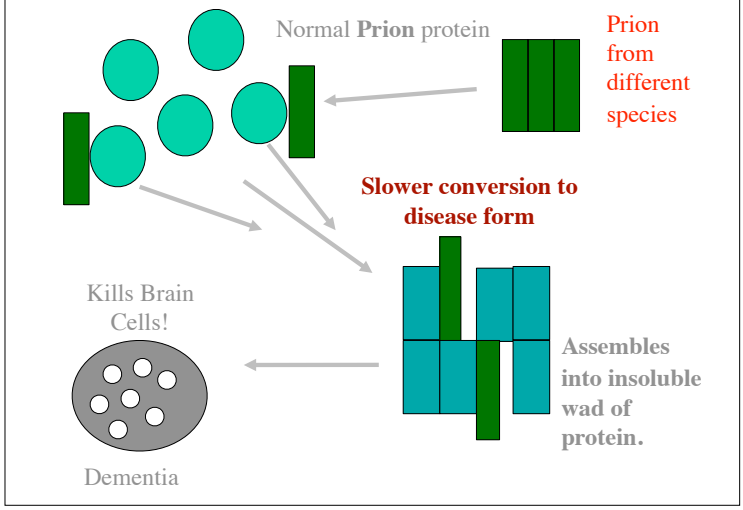




4 ways to get CJD:

1. Spontaneous misfolding of normal PrPc, which catalyzes misfolding of other PrPc proteins -> PrPsc.
2. Spontaneous mutation of PrPc gene, which causes expression of misfolding PrPsc.
3. Inheritance of PrPsc gene.
4. Ingestion of misfolded PrP proteins (which, being insoluble protein, survives digestion).

Species Barrier to Prion transmission



Species Barrier to TSE

the closer the species, the shorter the incubation time

PrPsc Species	Host Brain	Incubation time
hamster	hamster	77 days
hamster	mouse	> 700 days (mouse never gets it)
hamster	transgenic mouse w/ hamster PrPc	75 days

Sources of Human CJD

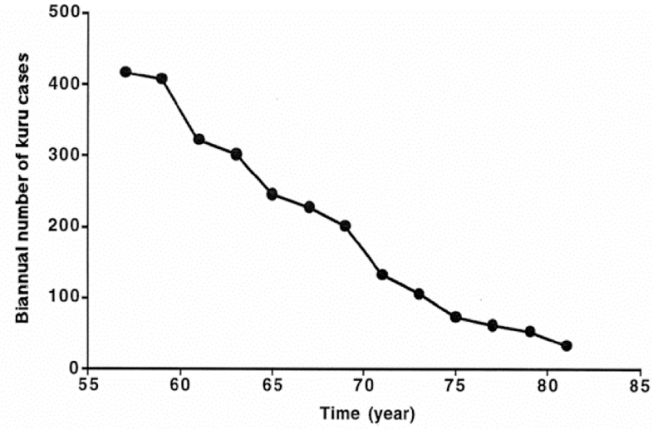
cannibalism

depth electrodes, cornea transplants, dura transplants

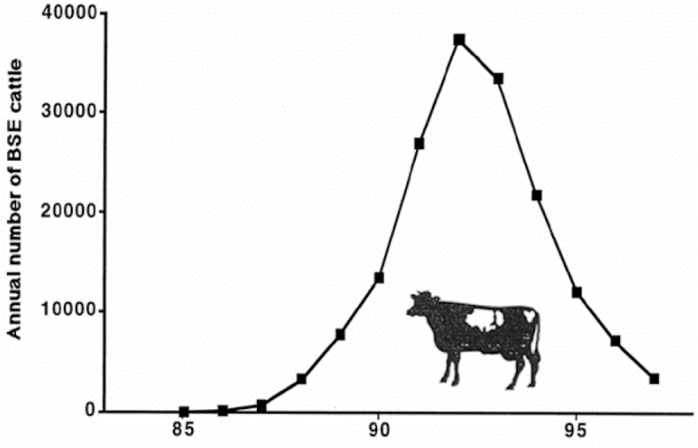
HGH and other pituitary extracts from cadavers

mad cow disease and other local items

Decline in Kuru



Rise and Fall of Mad Cow Disease



Bovine Spongiform Encephalopathy(BSE)

1. Originally thought to be caused by scrapie sheep -> meat and bone meal -> cow feed. Change in feed processing allowed scrapie prions -> cows -> feed -> more cows.
2. But: expts with sheep PrPsc –> cow brain do not replicate BSE (and no increase in scrapie in sheep or feed processing in other countries). Now thought that an animal alien to Britain got into the food chain.
3. Because sheep scrapie not transmissible to humans, British govt. did not respond quickly.

the rise and rise of BSE

22 Dec 1984: The first confirmed victim of BSE. Cow number 133 on the Stent farm in Sussex develops head tremors and a loss of coordination

11 Feb 1985: Cow 133 dies. Other cows show similar symptoms the next year

19 Sep 1985: Government pathologist finds Cow 133 died from spongiform encephalopathy (SE)

Nov/Dec 1986: Bovine spongiform encephalopathy (BSE) recognised as new cattle disease. Information placed "under embargo"

5 June 1987: Chief Veterinary Officer tells Ministry of Agriculture, Fisheries and Food (MAFF) of the new disease

5-6 Oct 1987: BSE found to be a prion disease. Described weeks later in *The Veterinary Record*

May 1998: Government forms Southwood working party to look into BSE

21 June 1988: BSE becomes notifiable disease

18 July 1988: Ruminant protein banned from sheep and cattle feed

9 Feb 1989: Southwood report says BSE is unlikely to pose threat to humans. Recommends setting up expert committee to advise on SE research

13 Nov 1989: Use of specified bovine offal (SBO) banned in human food

3 Feb 1990: BSE shown to be transferable from cow to cow by injection, and to mice orally

10 May 1990: Siamese cat called Max reported to have BSE-like disease. Species barrier appears to have been broken naturally

16 May 1990: Chief Medical Officer (CMO) says beef is safe to eat

4 March 1992: Spongiform Encephalopathy Advisory Committee (SEAC) says existing safeguards should protect human health

1992/1993: BSE peaks as 0.3 per cent of national herd affected. BSE starts to decline in 1993

11 March 1993: CMO again says beef is safe.

June 1994: BSE shown to be orally transferable from cow to cow

Source: New Scientist

May 1995: First death from variant CJD

Nov 1995: MAFF informs SEAC that some abattoirs are ignoring SBO ban. Infected tissue could still be entering human food chain

20 March 1996: SEAC announces probable link between BSE and vCJD

25 March 1996: EU bans British beef exports

3 April 1996: Cattle 30+ months banned from food chain

1 Aug 1996: MAFF says BSE may be passed from a cow to its calf

16 Aug 1996: Selective cull of cattle at most risk from BSE announced

16 Sep 1997: Mice studies reveal evidence for link between BSE and vCJD

22 Dec 1997: BSE Inquiry set up

26 Oct 2000: BSE Inquiry report published.
To date, 84 definite or probable cases of vCJD in Britain

Source: New Scientist

Nov 2000: First Spanish and German cases of BSE discovered

Feb 2000: Two Thai citizens reported to have vCJD, the first cases outside Europe

Aug 2002: First confirmed case of vCJD in North America

Feb 2003: Predicted deaths from vCJD slashed - a new analysis reduces the extent of the worst-case epidemic to 7000, following two years of falling figures

December 2003: The death of a British man from vCJD is linked to a blood transfusion seven years earlier

December 2003: First confirmed case of BSE in the US, in a cow slaughtered for food in Washington state earlier in the month.

November 2004: Study confirms that many people (60%) may have a genetic make-up that protects them against developing vCJD.

As of 2006: There have been 150 cases of vCJD in Britain, with only a few more worldwide, and it appears that only people with one genetic variant of the prion (40% of the population) develop the disease.

In 1997, the UK research group predicted that up to 10 million people could die from the devastating disease. In 2002, the figure dropped to 50,000. As of 2006, the likely upper limit of deaths has fallen to 7000.

Source: New Scientist

Bovine Spongiform Encephalopathy(BSE)

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5. 15 cases/yr -> 20,000 total vCJD. But cases/yr continue to rise, so likely to be > 136,000 cases (if confined to young people), even more if old people also susceptibile.

6. BSE may occur again outside Britain.

Future of Prions

Other prion diseases? Found in yeast and fungus, but none so far in mammals.

Treatments: none.

Under development:

Drugs that target conformation or block chain Rxn?

Transgenic sheep and cows resistant to PrPsc change.

USDA United States Department of Agriculture
Food Safety and Inspection Service

News Releases

Kansas Firm Recalls Cattle Heads That Contain Prohibited Materials

Recall Release
FSIS-RC-012-2008

CLASS II RECALL
HEALTH RISK: LOW

Congressional and Public Affairs
(202) 720-9113
Amanda Eamich

WASHINGTON, April 4, 2008 - Elkhorn Valley Packing LLC, a Harper, Kan., establishment, is voluntarily recalling approximately 406,000 pounds of frozen cattle heads with tonsils not completely removed, which is not compliant with regulations that require the removal of tonsils from cattle of all ages, the U.S. Department of Agriculture's Food Safety and Inspection Service announced today.

Tonsils are considered a specified risk material (SRM) and must be removed from cattle of all ages in accordance with FSIS regulations. SRMs are tissues that are known to contain the infective agent in cattle infected with BSE, as well as materials that are closely associated with these potentially infective tissues. Therefore, FSIS prohibits SRMs from use as human food to minimize potential human exposure to the BSE agent.

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Alzheimer's Disease

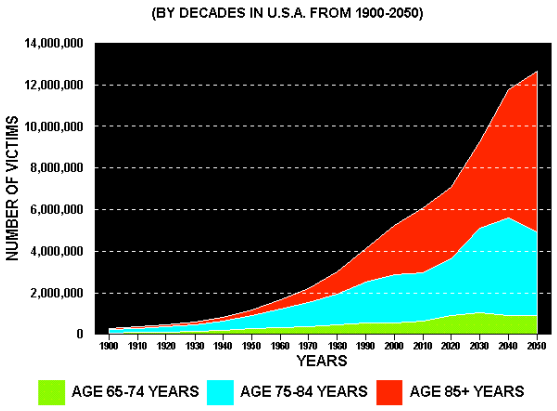
Alzheimer's disease is the most common cause of dementia in people age 65 and older.

Symptoms usually appear after age 60, although early-onset forms of the disease can occur, usually as the result of a defective gene.

Caused by the destruction of brain cells by plaques (clumps of a normally harmless protein called beta-amyloid) and tangles (fibrous tangles made up of an abnormal protein called tau protein).

Alzheimer's disease usually progresses slowly, over seven to 10 years, causing a gradual decline in cognitive abilities. Eventually, the affected part of the brain isn't able to work properly because of limited functions, including those involving memory, movement, language, judgment, behavior and abstract thinking.

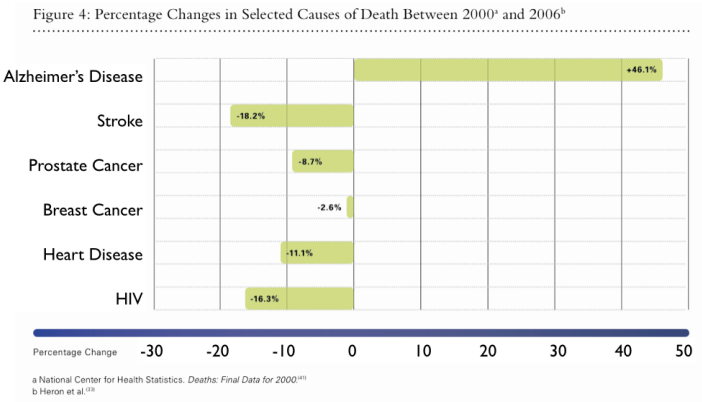
Prevalence of Alzheimer's Disease



Modified from: Brumback RA, Leech RW: Alzheimer's Disease: Pathophysiology and the hope for therapy. *Journal of the Oklahoma State Medical Association.* 1994; 87:103-111.

http://idi.ouhsc.edu/body.cfm?id=2875

Changes in Causes of Death



report_alzfactsfigures2010.pdf

Diagnosis of Alzheimer's Disease

Alzheimer's disease is progressive, resulting in impairment in cognitive function. The clinical symptoms associated with this disease include memory loss, language disorders, visuospatial impairment and behavioral disturbances. Alzheimer's may present with a variety of symptoms, but difficulties with memory are common to all.

For a diagnosis of probable Alzheimer's, the criteria adapted from the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) include:

- Dementia established by examination and objective testing
- Deficits in two or more cognitive areas
- Progressive worsening of memory and other cognitive functions
- No disturbance in consciousness
- Onset between ages 40 and 90

Absence of systemic disorders or other brain diseases, which could account for the deficits in memory and cognition, should also be established. Atypical cases of dementia should be referred to specialists for assessment.

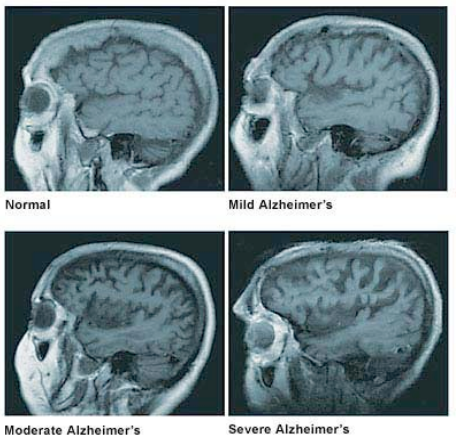
http://www.alz.org/professionals_and_researchers_diagnostic_procedures.asp

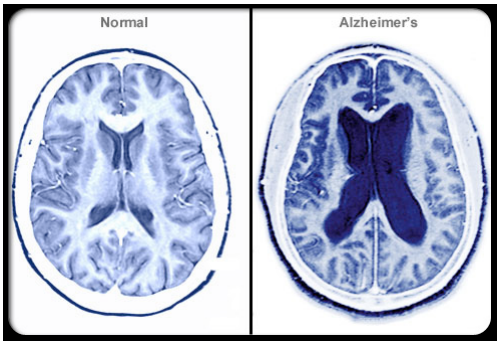
Warning Signs of Alzheimers

1. Memory changes that disrupt daily life.
2. Challenges in planning or solving problems.
3. Difficulty completing familiar tasks at home, at work or at leisure
4. Confusion with time or place.
5. Trouble understanding visual images and spatial relationships.
6. New problems with words in speaking or writing
7. Misplacing things and losing the ability to retrace steps
8. Decreased or poor judgment
9. Withdrawal from work or social activities.
10. Changes in mood and personality

But no good biomarker test for early detection of Alzheimers

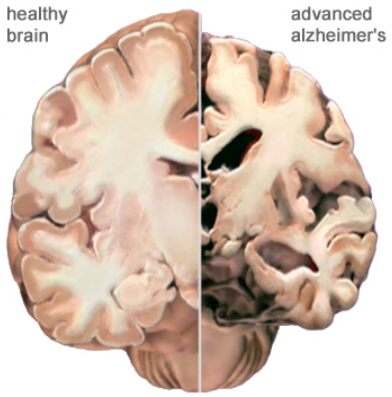
http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp?type=more_informatio





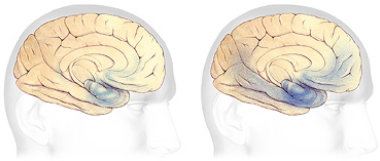
Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain. As the disease progresses, brain tissue shrinks and the ventricles (chambers within the brain that contain cerebrospinal fluid) become larger. The damage disrupts communication between brain cells, crippling memory, speech, and comprehension.

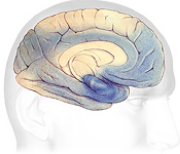
WebMD http://www.medicinenet.com/alzheimers_disease_pictures_slideshow/article.htm



http://www.alz.org/alzheimers_disease_4719.asp

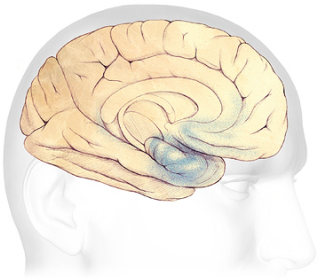
Stages of Alzheimers





- **Earliest Alzheimer's** – changes may begin 20 years or more before diagnosis.
- **Mild to moderate Alzheimer stages** – generally last from 2 - 10 years.
- **Severe Alzheimer's** – may last from 1 - 5 years.

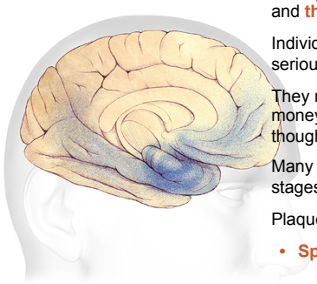
Stages of Alzheimers



In the earliest stages, before symptoms can be detected with current tests, plaques and tangles begin to form in brain areas involved in:

- **Learning and memory**
- **Thinking and planning**

Stages of Alzheimers



More plaques and tangles develop in regions of **memory** and **thinking and planning**.

Individuals develop problems with memory or thinking serious enough to interfere with work or social life.

They may also get confused and have trouble handling money, expressing themselves and organizing their thoughts.

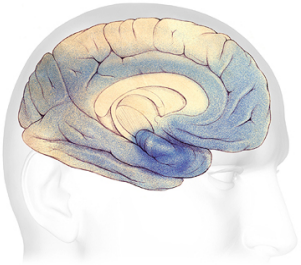
Many people with Alzheimer's are first diagnosed in these stages.

Plaques and tangles also spread to areas involved in:

- **Speaking and understanding speech**
- **Sense of where the body is in relation to objects around it**

As Alzheimer's progresses, individuals may experience changes in personality and behavior and have trouble recognizing friends and family members.

Stages of Alzheimers

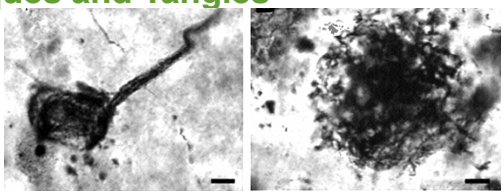


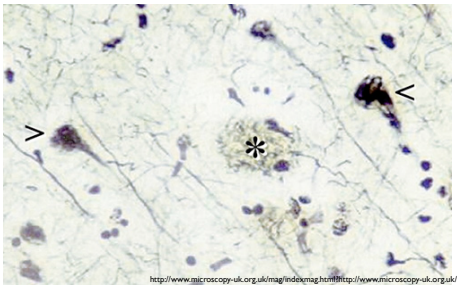
In advanced Alzheimer's disease, most of the cortex is seriously damaged.

The brain shrinks dramatically due to widespread cell death.

Individuals lose their ability to communicate, to recognize family and loved ones and to care for themselves.

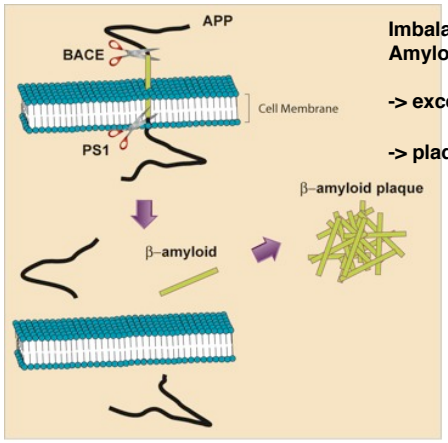
Plaques and Tangles





http://www.microscopy-uk.org.uk/mag/indexmag.html?http://www.microscopy-uk.org.uk/mag/artsep06/mc-Alzheimer.html

Beta Amyloid and Plaques



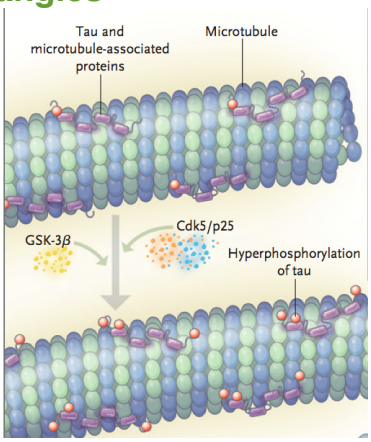
Imbalance in processing of Amyloid Precursor Protein (APP)

-> excess beta-amyloid

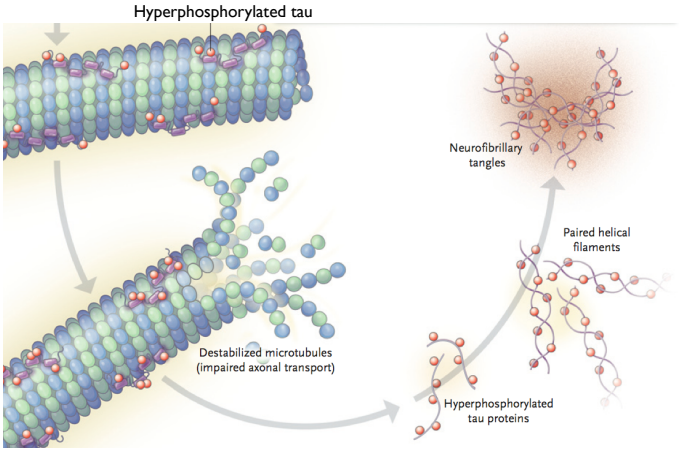
-> plaque formation

http://biosingularity.wordpress.com/2006/09/15/caffeine-reduces-the-rish-of-alzheimers-disease/

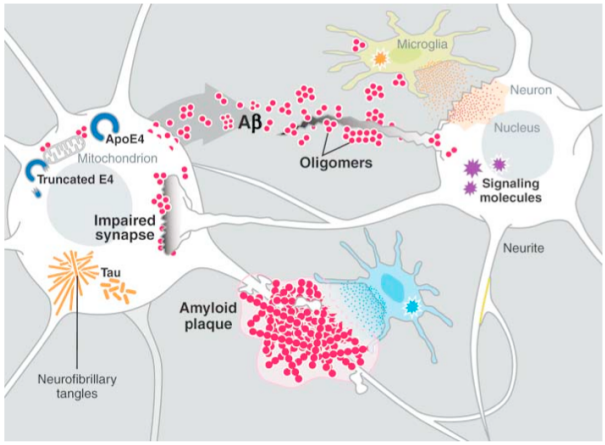
Tau and Tangles



Tau and Tangles



Plaques and Tangles



Genetics of Alzheimers

Early Onset Alzheimers (30-60 y.o.)

Amyloid Precursor Protein mutations
Presenilin 1, Presenilin 2 (enzymes that process APP)

Late-Onset Alzheimers (65+ y.o.)

Apolipoprotein E4 (ApoE4)
Cholesterol binding protein;
Risk of late-onset Alzheimer's increases with copies of ApoE4;
promotes Beta Amyloid and Tau injury

Treatments

Cholinesterase inhibitors

Increase acetylcholine levels in the cortex, boost memory

Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne)

Memantine (Namenda)

Boosts glutamate levels

http://www.alz.org/alzheimers_disease_treatments.asp