About Alzheimer's

Dedicated to my mother,
An Alzheimer's Victim

“DEMENTIA” is a term that is often used inappropriately.

Dementia is not a disease but rather it is a term that refers to a set of symptoms that in turn are caused by an overlying disease such as Alzheimer’s. Dementia symptoms are not early stage symptoms in the disease, but rather are symptoms that appear in middle and late stages. Examples of other dementia causing diseases would be Lewy Body, Vascular Dementia, and Fronto Temporal lobe Dementia.

Condition	Pathological Markers	Main areas affected
Alzheimer's disease	Amyloid plaques, neurofibrillary tangles	Cerebral cortex, hippocampus, basal nucleus of Meynert
Lewy body dementia	Lewy bodies	Cerebral cortex, substantia nigra, basal nucleus of Meynert
Parkinson's disease	Lewy bodies	Substantia nigra, dorsal motor nucleus of the vagus, basal nucleus of Meynert
Vascular dementia	Vascular infarctions, atherosclerosis, and other markers of vascular disease	Cerebral cortex, hippocampus
Progressive supranuclear palsy	Neurofibrillary tangles	Cerebral cortex, basal ganglia, spinal cord, midbrain
Corticobasal degeneration	Ballooned neurons with tau inclusions	Cerebral cortex, basal ganglia
Multiple system atrophy	Alpha-synuclein inclusions	Hindbrain structures involved in balance and autonomic functions

Evidence of the existence of Alzheimer's and other dementia type diseases can be found in the early day writings of Authors, Poets, Philosophers and Historians. The recorded evidence in the writings go back almost a thousand years before the birth of Christ and continues uninterrupted into modern day history.

Plato (Ca. 428-347 BC) insisted that those suffering from "the influence of extreme old age" should be excused of their crimes.

Cicero (106-43 BC) talked of
the folly of "frivolous old men."

Shakespeare gave a perfect description of Alzheimer's in his rendition of "King Lear."

"Pray, do not mock me: I am a very ...old man,...Fourscore and upward, not an hour more nor less; And, to deal plainly, I fear I am not in my perfect mind. Methinks I should know you, and know this man; Yet I am doubtful for I am mainly ignorant What place this is; and all the skill I have remembers not these garments; nor I know not Where I did lodge last night. Do not laugh at me;"

(William Shakespeare (1605) King Lear, Act IV, Scene 7.)

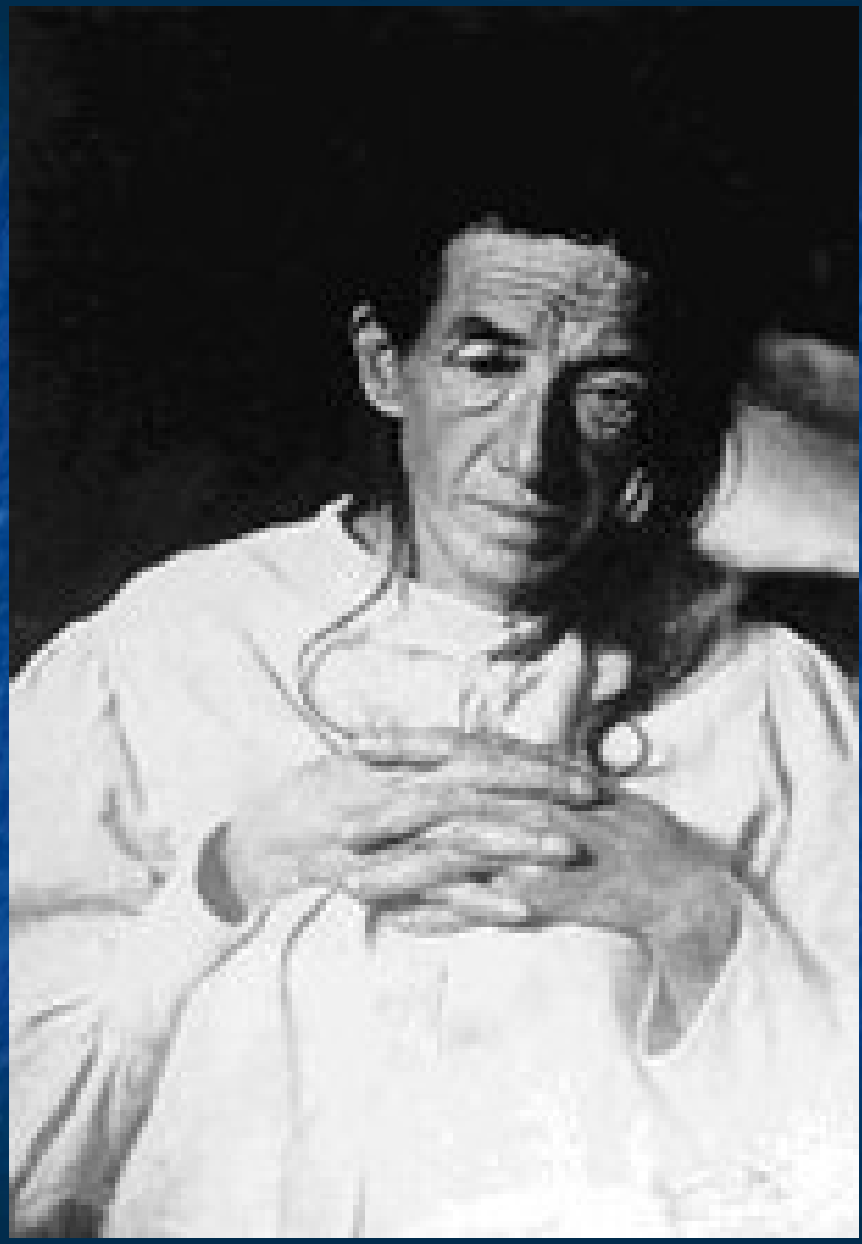
Alzheimer's disease is a brain disorder named after German physician Alois Alzheimer, who first described it in 1906.

In 1901, a 51-year-old female patient from Frankfurt, Germany was brought to Dr. Alzheimer.

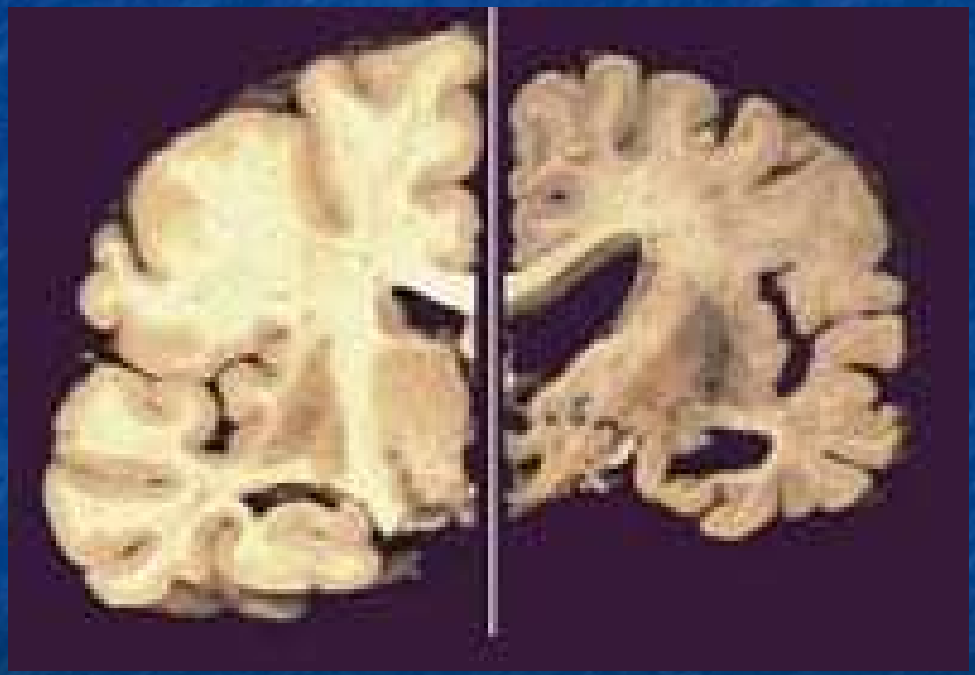
The patient, Frau Auguste Deter had developed memory problems, unfounded suspicions that her husband was unfaithful, and difficulty speaking and understanding what was said to her.

Her symptoms rapidly grew worse, and within a few years she was bedridden.

In 1906, Frau Auguste Deter died of complications from her condition.

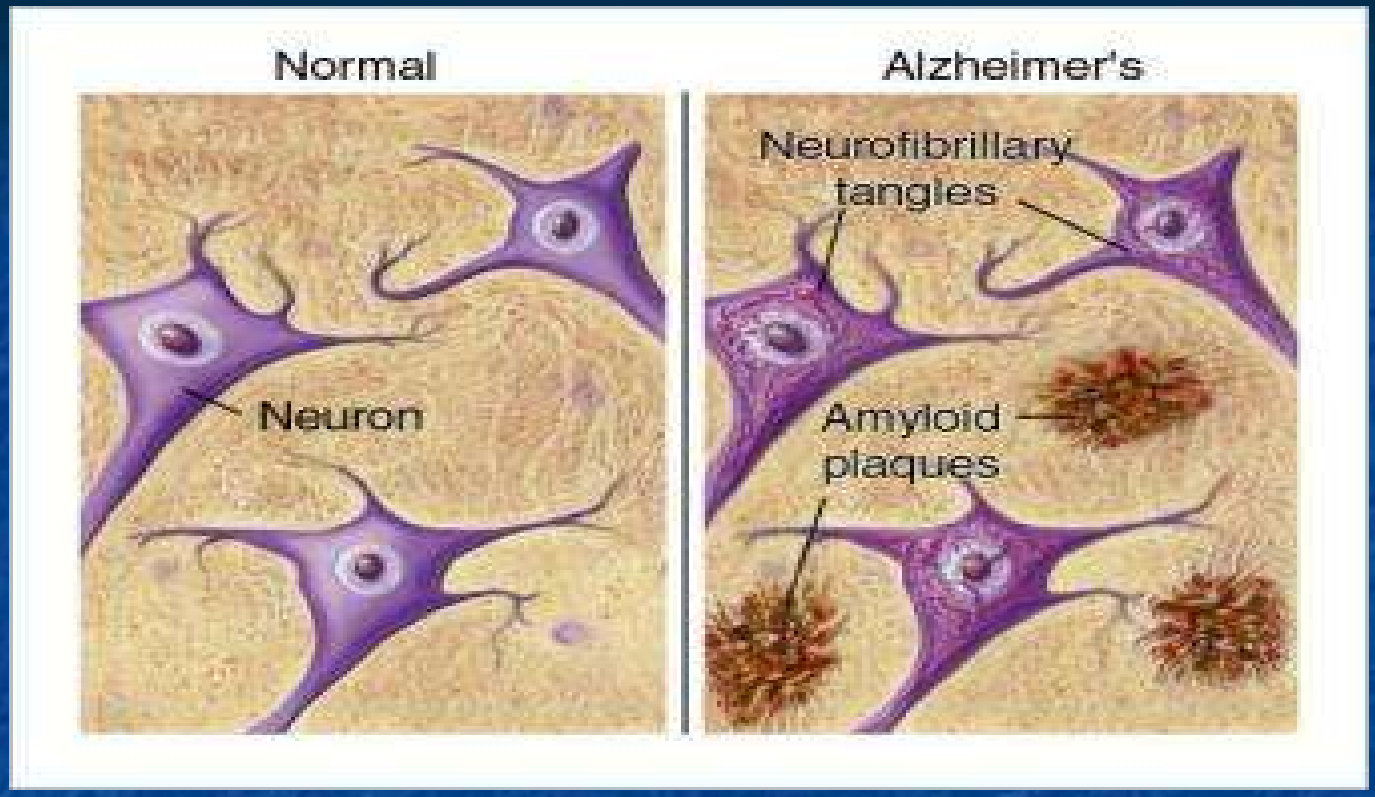


In an autopsy of the patient's brain, he saw dramatic shrinkage, especially of the cortex, the outer layer involved in memory, thinking, judgment and speech.



Normal Brain

Brain of an Alzheimer's Patient



Under the microscope, there were widespread fatty deposits in small blood vessels, dead and dying brain cells, and abnormal protein amyloid deposits and tangles (Tau) in and around the dying neuron brain cells.

For many centuries, mankind suffered with the symptoms of this terrible disease, before Alzheimer's was finally recognized as a disease and named as such!

Alzheimer's is a disease of the brain that causes a steady decline in memory and other brain functions.

The brain cells (Neurons) begin to die.

This eventually results in *dementia symptoms severe enough to interfere with everyday life.

*Dementia is not a disease of itself but rather it is a group of symptoms. It is a loss of intellectual functions such as thinking, remembering and reasoning. Some overlying disease is the cause of the dementia symptoms.

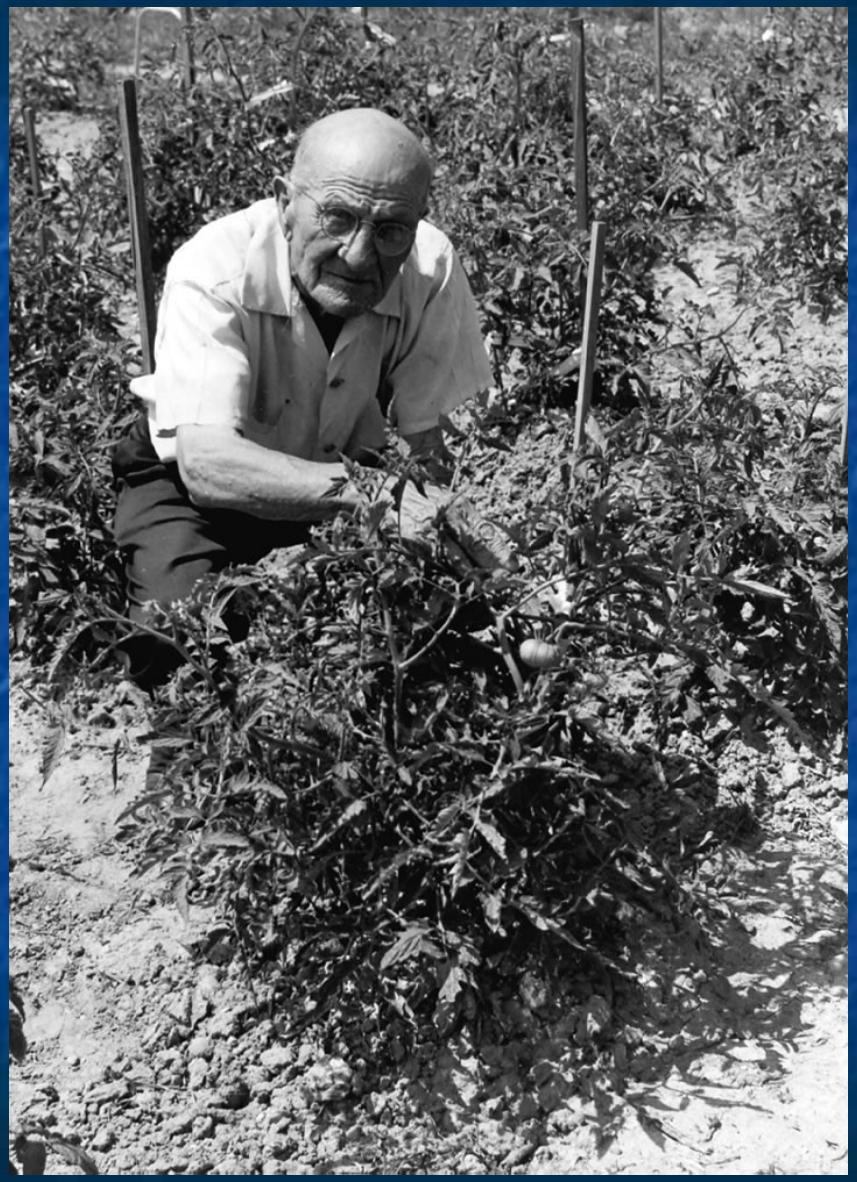
More than 5.4 million Americans
now have Alzheimer’s Disease.

Alzheimer's has no cure.

Alzheimer's is the only disease among the top 10 in the mortality tables that has not had a rate decline, but instead has seen a rapid rate escalation.

Alzheimer's is the fifth leading cause of disease death in the U.S.

Alzheimer's is the fourth leading cause of death for those over 65.



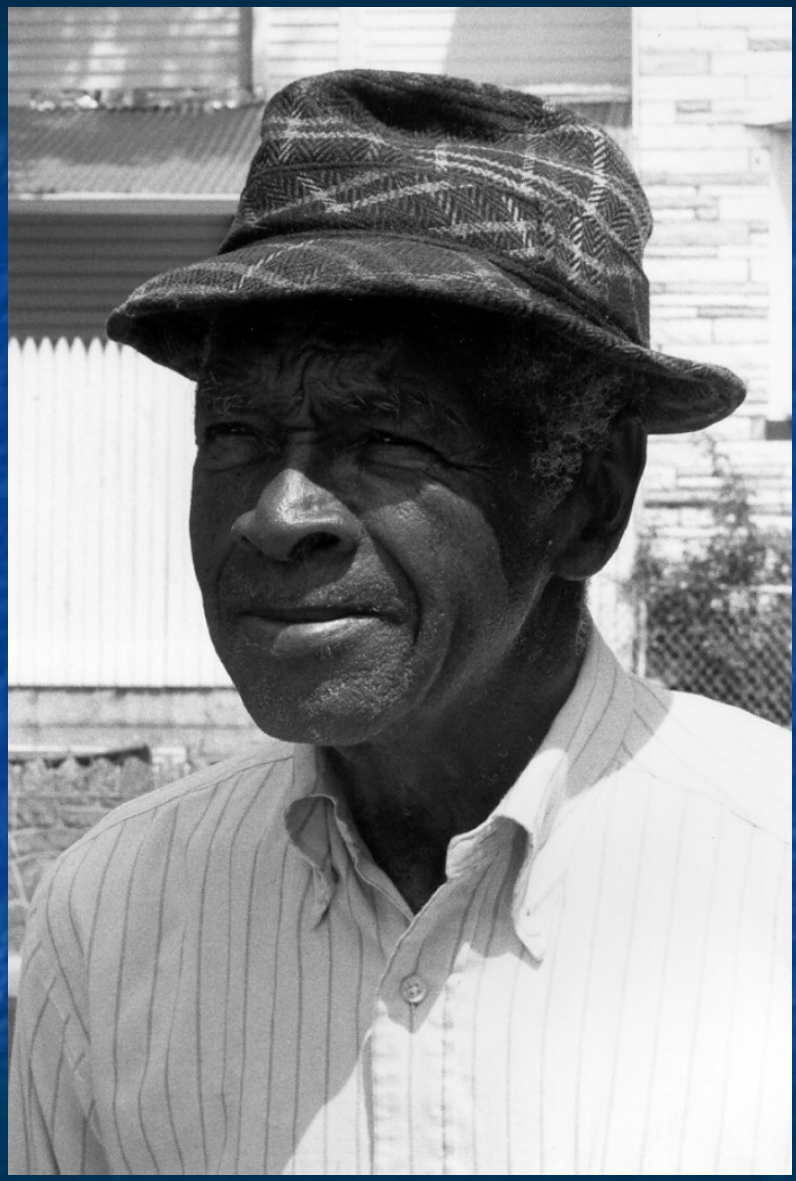
An Alzheimer victim will live an average of eight years from the time of diagnosis.

Without a cure,
the prevalence of
Alzheimer's Disease
will dramatically escalate
as the 78 million
baby boomers age.

“DEMENTIA” is a term that is often used inappropriately.

Dementia is not a disease but rather it is a term that refers to a set of symptoms that in turn are caused by an overlying disease such as Alzheimer’s. Dementia symptoms are not early stage symptoms in the disease, but rather are symptoms that appear in middle and late stages. Examples of other dementia causing diseases would be Lewy Body, Vascular Dementia, and Fronto Temporal lobe Dementia.

Alzheimer's disease accounts for about 70-80% of all dementia symptoms.



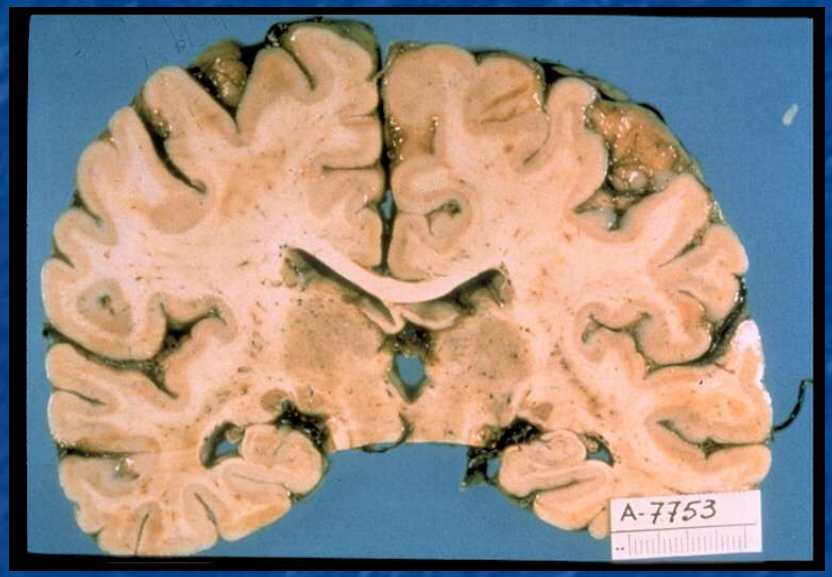
Signs & Symptoms:

- Memory loss for recent events
- Progresses into dementia → almost total memory loss
- Inability to converse, loss of language ability
- Affective/personality disturbance (fatuous, hostile)
- Death from opportunistic infections, etc.

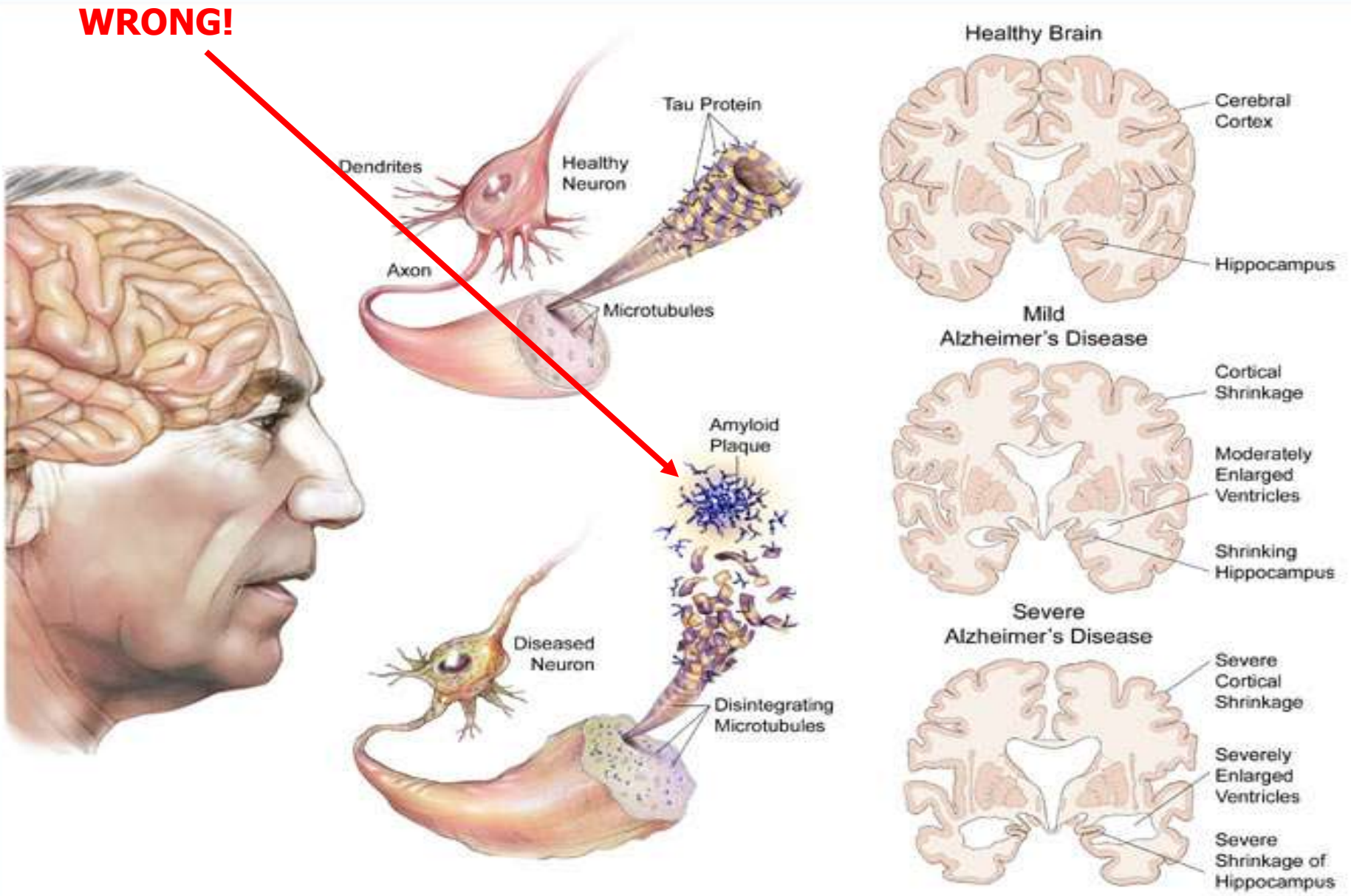
Confirmation of Diagnosis:

- Neuronal (amyloid, β amyloid, Aβ amyloid) plaques
- Neurofibrillary tangles
- Brain Atrophy

Brain Scan



Brain Atrophy in AD



Two Major Hypotheses for AD:

β amyloid protein (BAP) v. tau

1. **BAPists: The accumulation of a fragment of the amyloid precursor protein or APP (the amyloid beta 42 residue fragment or Ab-42) leads to the formation of plaques that kill neurons.**

2. **TAUists: Abnormal phosphorylation of tau proteins makes them "sticky," leading to the break up of microtubules. The resulting loss of axonal transport causes cell death.**

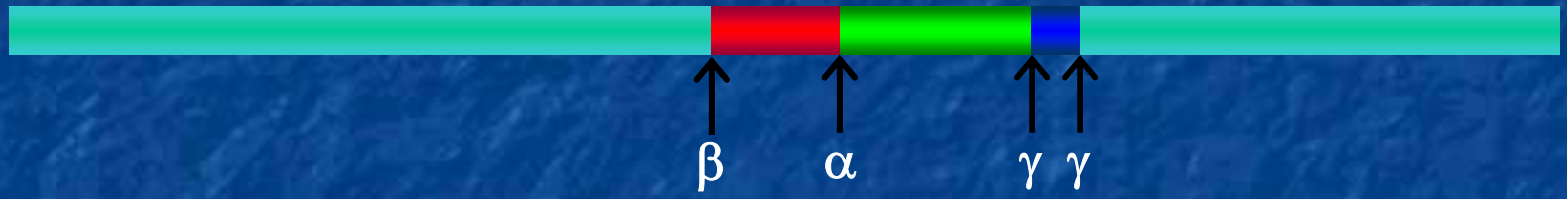
Amyloid Hypothesis

(it's the plaques, dummy)

1. The nonsoluble or "sticky" nature of Aβ-42 helps other protein fragments (including apoE) to gather into plaques.
2. Somehow the plaques (or possible the migration of Aβ-42 outside the cell) cause neuronal death.
3. The amyloid precursor protein (APP) is broken down by a series of secretases .
4. During this process, a nonsoluble fragment of the APP protein (called Aβ-42) accumulates and is deposited outside the cell.
5. PSEN1 & PSEN2 genes → subunits of γ secretase.

β-secretase Pathway:
(not drawn to scale)

APP Protein:



(1) β-secretase cuts APP protein, giving:

(2) γ-secretase cuts this residue, giving:

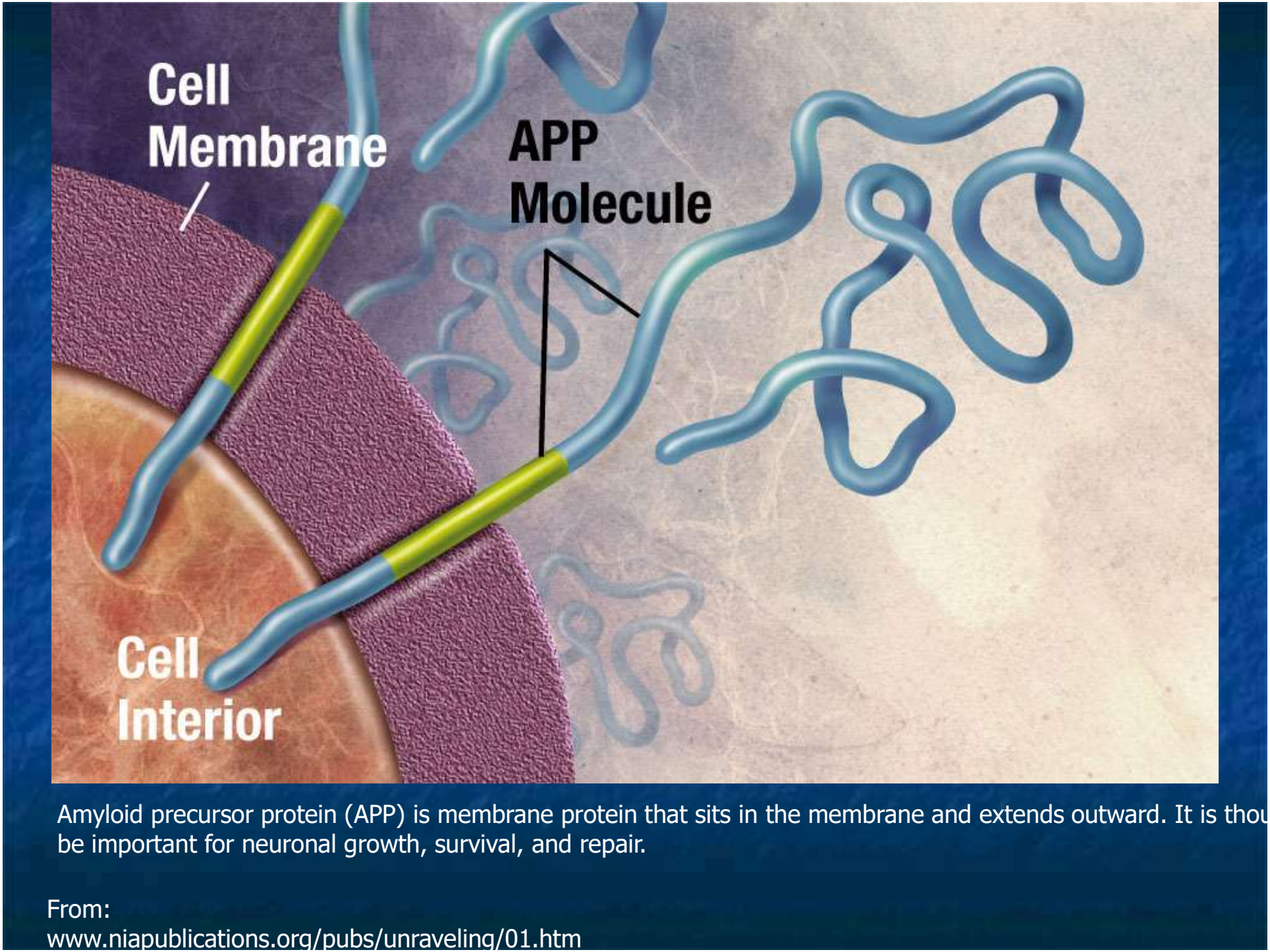
Aβ40 Fragment

Soluble

or

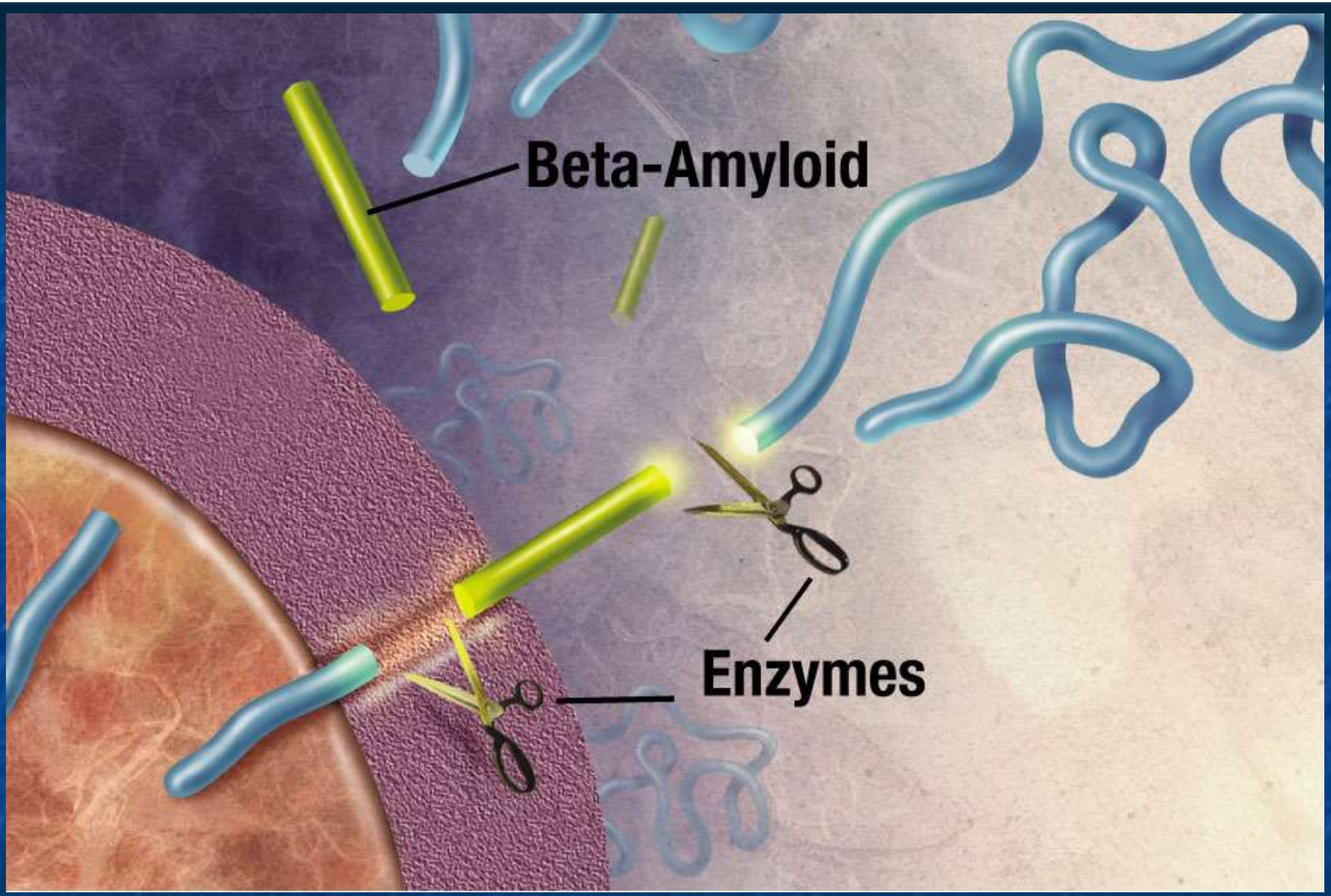
Aβ42 Fragment

Unsoluble, aggregates into plaques



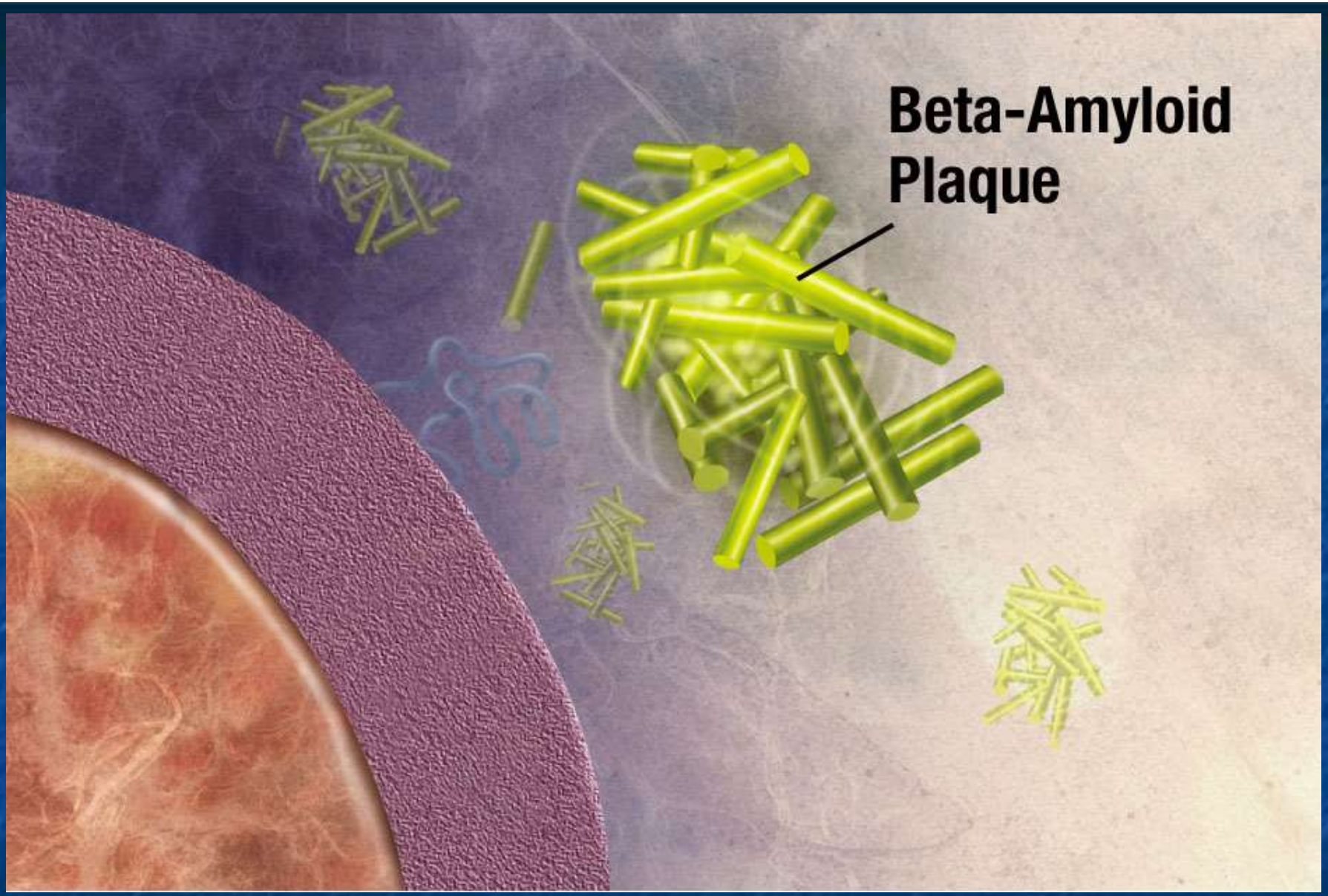
Amyloid precursor protein (APP) is membrane protein that sits in the membrane and extends outward. It is thou
be important for neuronal growth, survival, and repair.

From:
www.niapublications.org/pubs/unraveling/01.htm



Enzymes cut the APP into fragments, the most important of which for AD is called β-amyloid (beta-amyloid) or Aβ.

From:
www.niapublications.org/pubs/unraveling/01.htm



Beta-amyloid is "sticky" so the fragments cling together along with other material outside of the cell, forming th plaques seen in the AD brain.

From:
www.nianublications.org/pubs/unraveling/01.htm

Tau Hypothesis
(it's the tangles, dummy)

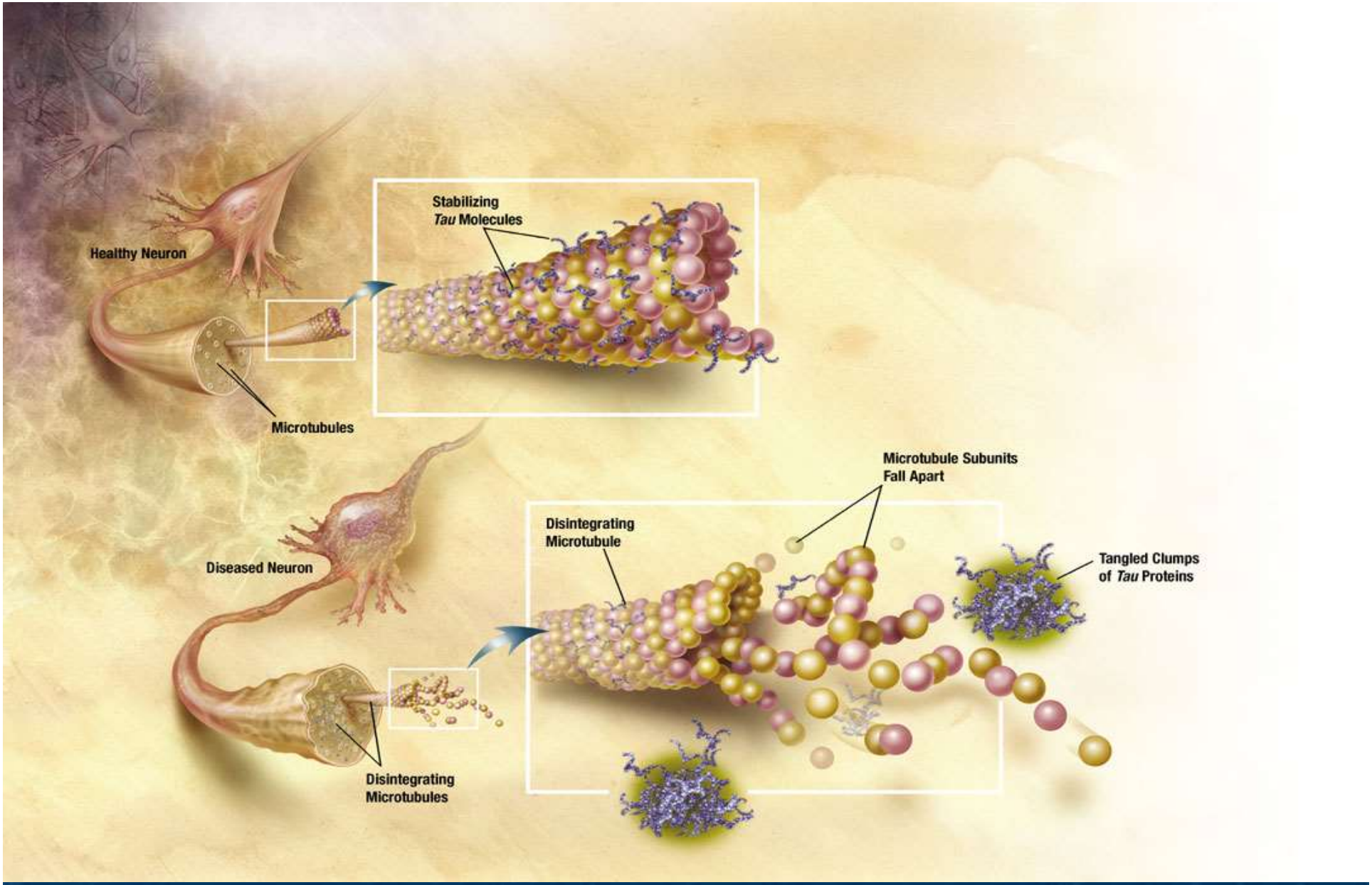
1. Ordinarily, the τ (tau) protein is a microtubule-associated protein that acts as a three-dimensional "railroad tie" for the microtubule. The microtubule is responsible for axonal transport.

2. Accumulation of phosphate on the tau proteins cause "paired helical filaments" or PHFs (like two ropes twisted around each other) that accumulate and lead to the neurofibrillary tangles (NFT). PHFs are the main component in NFTs.

3. Impaired axonal transport is the probable cause of cell death.

4. Focus on MAPT gene (microtubule-associated protein tau)

5. Not in favor anymore.



Microtubules are like railroad tracks that transport nutrition and other molecules. Tau-proteins act as "ties" that stabilize the structure of the microtubules. In AD, tau proteins become tangled, unstabilizing the structure of the microtubule. Loss of axonal transport results in cell death.

Current theory: Multifactorial, involving several pathways.

- Protein accumulation: → placques & tangles
- Inflammation: Unregulated activation of glia
- Lipid distribution: Lipid membrane site of APP cleavage.
- Reduction of Acetylcholine levels

Multifactorial Threshold Model

- Many common alleles with "low" penetrance.
- Most people will have several risk alleles.
- Risk alleles are additive (multiplicative).
- Many additive environmental factors.
- Genes and environment → ***liability***.
- Once liability reaches a certain value (i.e., the ***threshold***) a disease process begins.

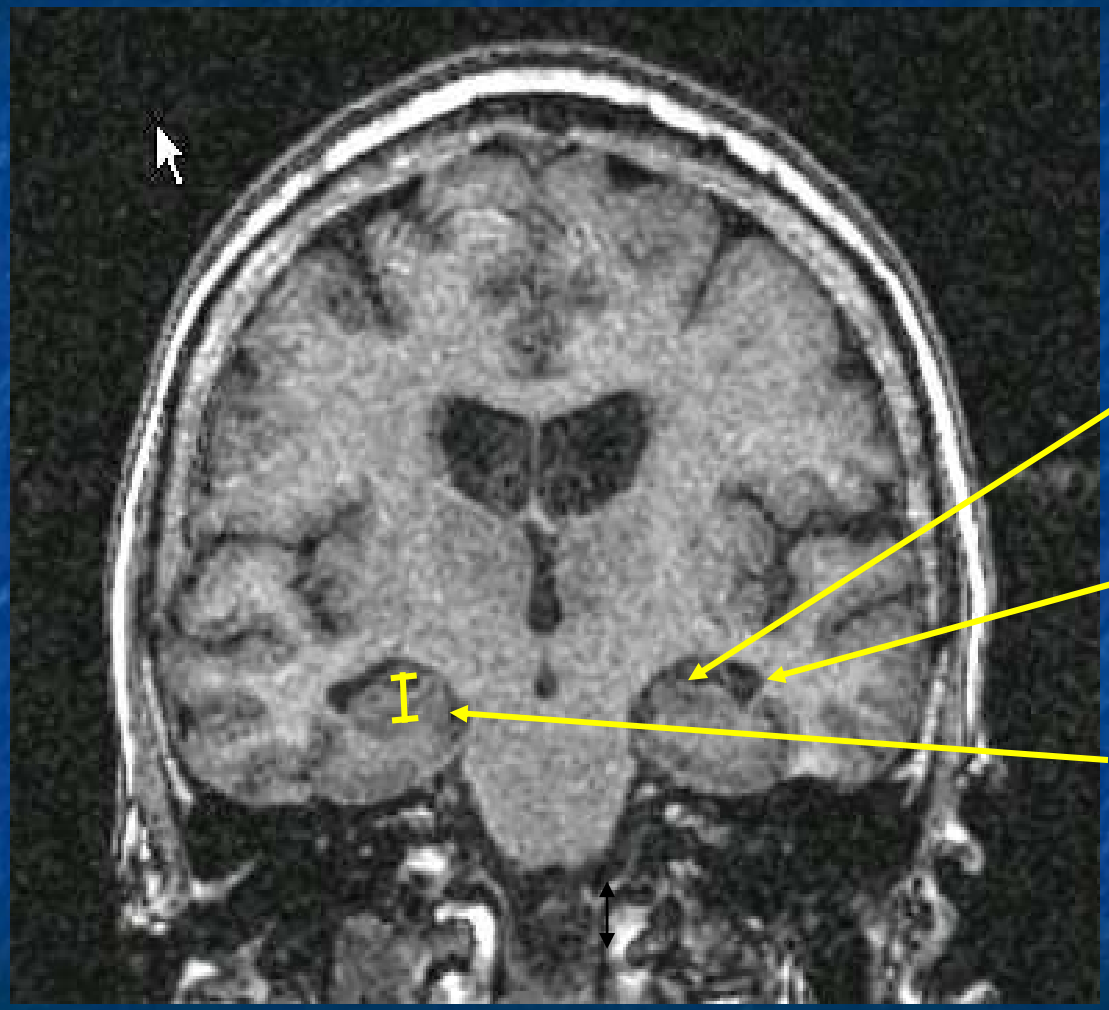
DIAGNOSIS OF AD

1) Specific memory tests

Dubois and Albert, Lancet Neurology, 2004

- Very poor free recall
- Decreased total recall (free+cued) because an insufficient effect of retrieval facilitation with **cueing**

2) A specific profile of MTL atrophy on MRI



Atrophy in Alzheimer's disease

Prodromal AD	15%
Mild dementia	25%
Moderate dementia	40%

Choroid fissure

Temporal horn

Height of the hippocampus

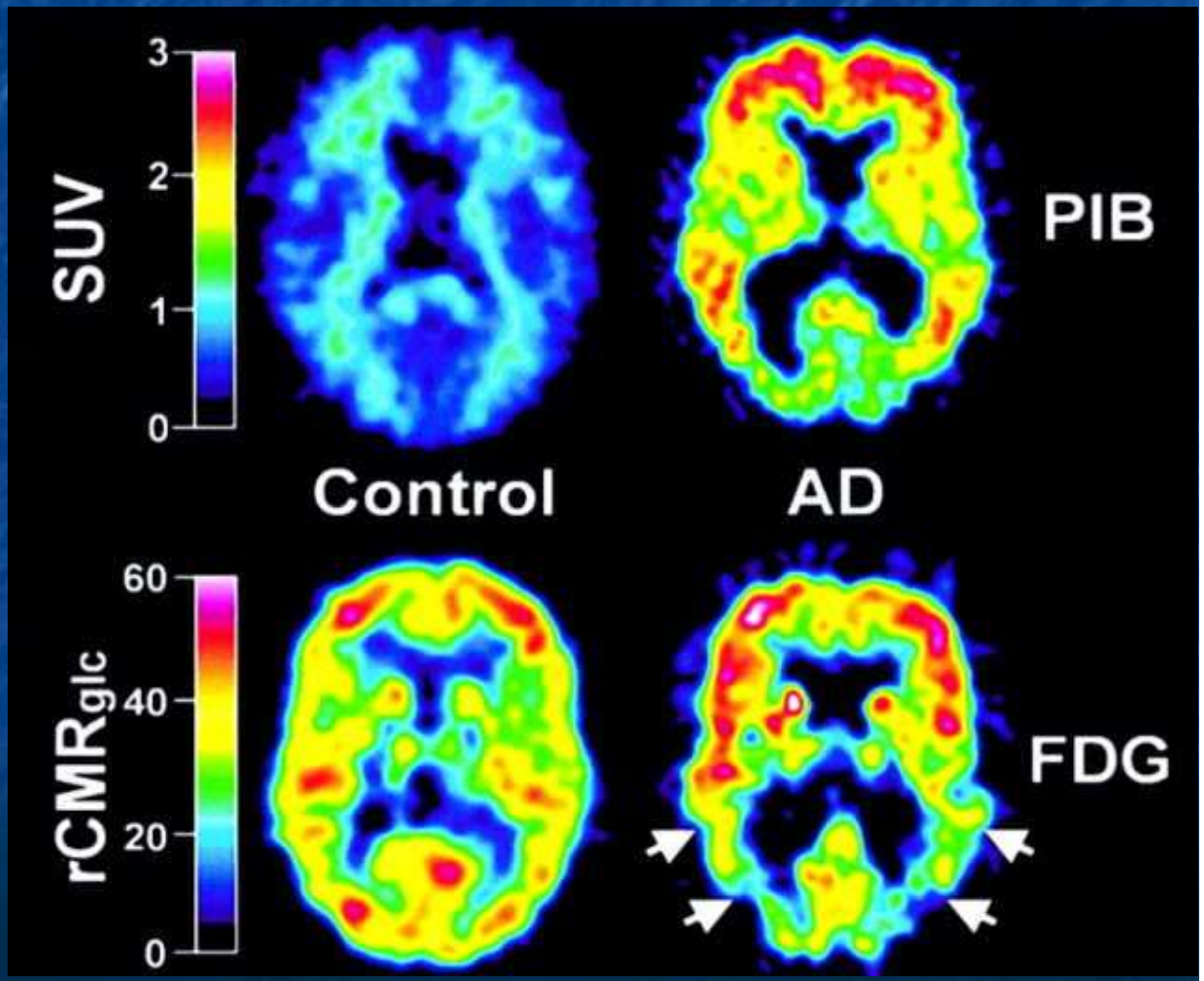
Qualitative MTL Rating Scale
Scheltens, JNNP 1992

3) PET imaging

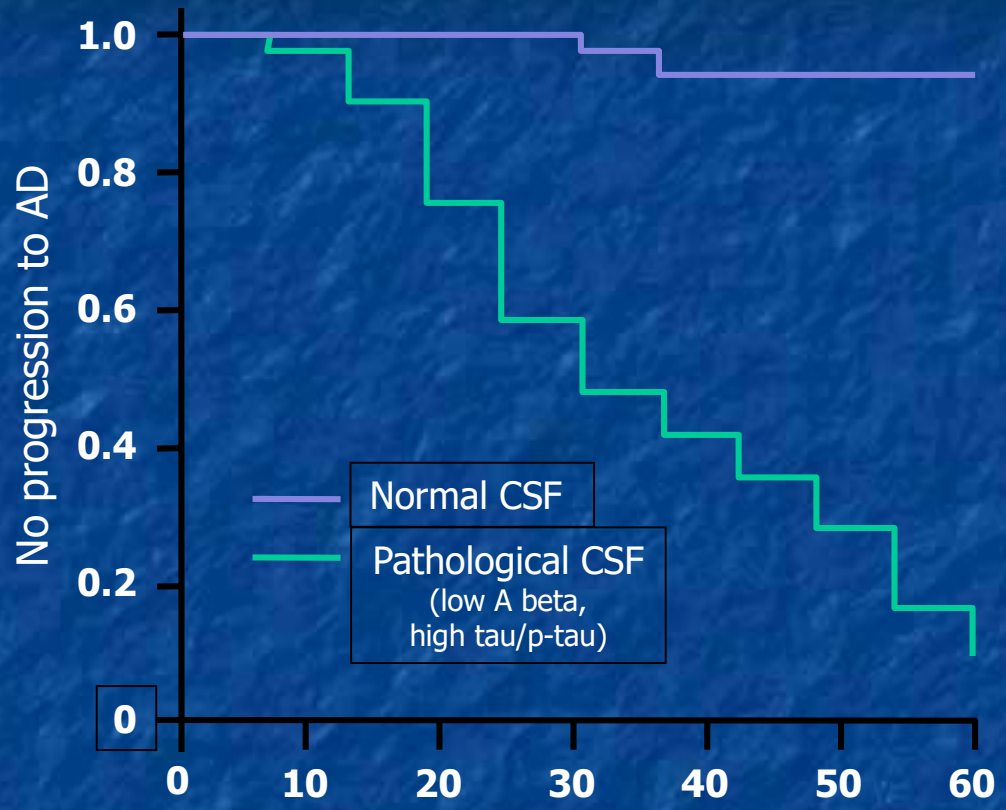
A specific pattern in Molecular Neuroimagery

- ***PET-FDG.*** Pooled sensitivities and specificities (9 studies) of 86% for temporo-parietal hypometabolism (***Patwardhan, 2004***)

- ***PET-PiB.*** Increased radioligand retention in AD compared to control subjects (***Klunk, 2004***)



4) specific pattern of CSF changes (low A beta; high tau and P-tau levels) even at an eary stage



Normal CSF	67	66	62	56	47	40	28
Pathological CSF	67	65	49	31	27	15	3

(Hansson et al. LN, 2006)

In April 2011, new Criteria and Guidelines for Alzheimer's Disease diagnosis were established by a work group of the National Institute on Aging (NIA) of the National Institute of Health (NIH) and the Alzheimer's Association.

This work group established the following 3 stages of Alzheimer's Disease:

1. Pre-Clinical Alzheimer's Disease. (Prior to symptoms) This stage is presently reserved for research purposes only.
2. Mild Cognitive Impairment due to Alzheimer's Disease.
3. Dementia due to Alzheimer's Disease.

2011

NIA/AD diagnostic Criteria

3 stages

- AD dementia stage
- MCI stage
- Preclinical stage

Progressive Stages of Alzheimer's Disease

Stage 1. (Early or Mild):

- Short term memory problems
- May be unable to find the right words
- Forgets familiar names and telephone numbers
- Begins to write reminders but loses notes
- Shows preference for familiar things
  (Wears the same clothes, Avoids going out)
- Judgment may be impaired
  (May dress inappropriately for the weather)

Progressive Stages of Alzheimer's Disease

Stage 2a. (Middle or Moderate):

- Deterioration of ability to initiate and sequence purposeful activities like bathing and driving
- Sleep disturbance with restlessness at night
- Begins to neglect health and hygiene
- Needs directions to function in familiar surroundings

Progressive Stages of Alzheimer's Disease

Stage 2b. (Middle or Moderate):

- May lose ability to perform daily skills (like buttoning a shirt or using a knife & fork)
- May need to be told each step of a former routine act (like brushing teeth or getting dressed)
- May walk with a shuffling gait or may seem "glued to the floor" due to a physical inability to walk
- Often needs physical assistance with activities of daily living (dressing, bathing, eating)
- Needs protection and supervision
- May lose the ability to read or write

Progressive Stages of Alzheimer's Disease

Stage 3. (Late or Final):

- Can't walk
- May discontinue talking or be unable to talk
- Trouble swallowing
- May have seizures
- Incontinence
- May make loud unintelligible negative noises or sounds
- Complete withdrawal or apathy
- May lose control of outer extremities
- Unable to survive without total care

Delirium, Depression, and Dementia

- Delirium
  - Acute onset, can be treated
  - Altered state of consciousness
- Depression
  - Gradual onset, can be treated
  - Look for signs, such as low self-esteem
- Dementia
  - Gradual onset, might be treated
  - Memory loss and decline in cognitive function

Treatment Modalities

- 1. Behavioral
- 2. Physical
- 3. Pharmacological

Treatment of neurodegenerative diseases

- Currently available drugs for the treatment of AD are purely for symptoms and among these drugs are the cholinesterase inhibitors.

- After acetylcholine is released from the synapse, cholinesterase inhibitors delay its degradation, leading to improved cognition. However, these types of drugs have only a modest effect, which can be variable among patients.
- Another type of drug available for AD patients is an *N*-methyl-D-aspartate (NMDA) receptor antagonist named memantine.
- Memantine prevents the NMDA receptors from overstimulation that can lead to toxicity. Since the current treatments have only marginal effects and greatly vary in their effectiveness in patients, the need for new treatments is great.

*Roberson ED, Mucke L: Science 2006, **314:**781-784.*

Medications

- Cholinesterase Inhibitors
  - DONEPEZIL
  - RIVASIGMINE
  - GALANTAMINE
- Glutamate Receptors
- MEMANTINE

Anti-Inflammatory and Antioxidative Activites

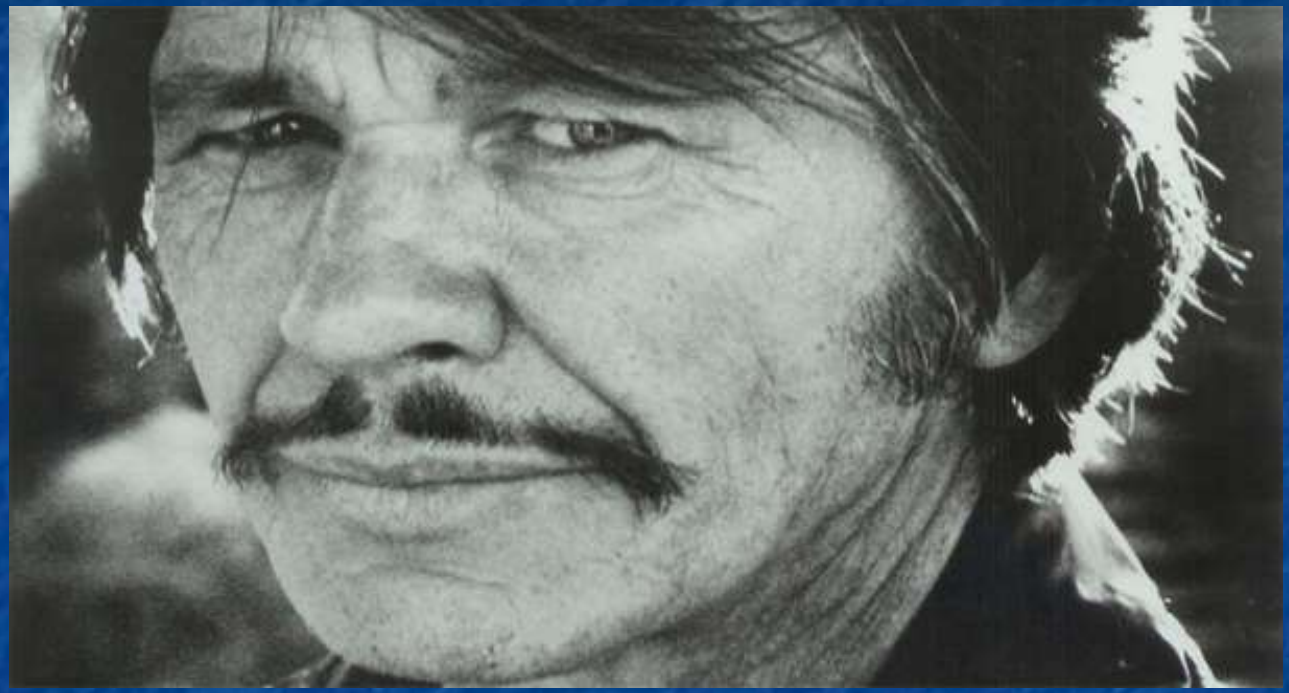
- Various medicinal plants have anti-inflammatory activities by inhibiting cyclooxygenase-1 (COX-1) that surrounds amyloids plaque in microglia. The accumulation of COX-1 enzyme in microglia in AD patients may be responsible for the local increase in oxidative stress and prostaglandin synthesis .
- Ferula assafoetida, Syzygium aromaticum, and Zingiber officinalis have previously been reported to have activity against COX-1 enzyme .
- F. assafoetida has previously been used as memory enhancer, antibacterial, antispasmodic, and antihelminthic in traditional medicines. Z. officinalis showed not only anti-COX-1 activity but also free radical scavenging activity that may be contributed to the presence of important phytochemicals such as gingerols and shogaols .

Anti-Inflammatory and Antioxidative Activites

- Sinapic acid (Brassicaceae) shows anti-inflammatory activity and can act as a neuroprotective agent by decreasing the levels of Aβ and by protecting neuronal cell death .
- On the other hand, Emblica officinalis may be used in the treatment of mental disorders and as anti-inflammatory agent. Several natural polyphenols such as vitamins, flavonoids, phenolic acids, and other polyphenols including thymol, ellagic acid, and eugenol have antioxidant properties and may be used for neurodegenerative diseases as promising therapeutic agents

S. K. Ali et al., *BMC Complementary and Alternative Medicine*, vol. 13 article 121, 2013.

Well known public figures
and celebrities
who are victims of
Alzheimer's…



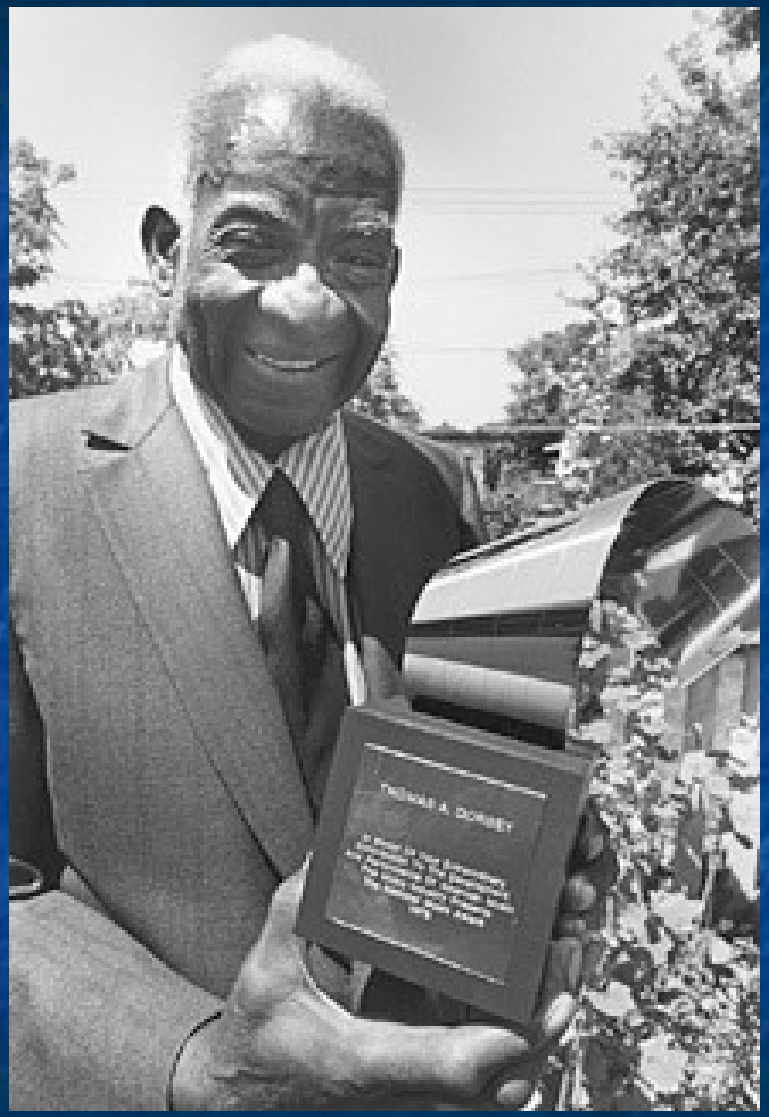
Charles Bronson

Actor, Film Director

Thomas Dorsey

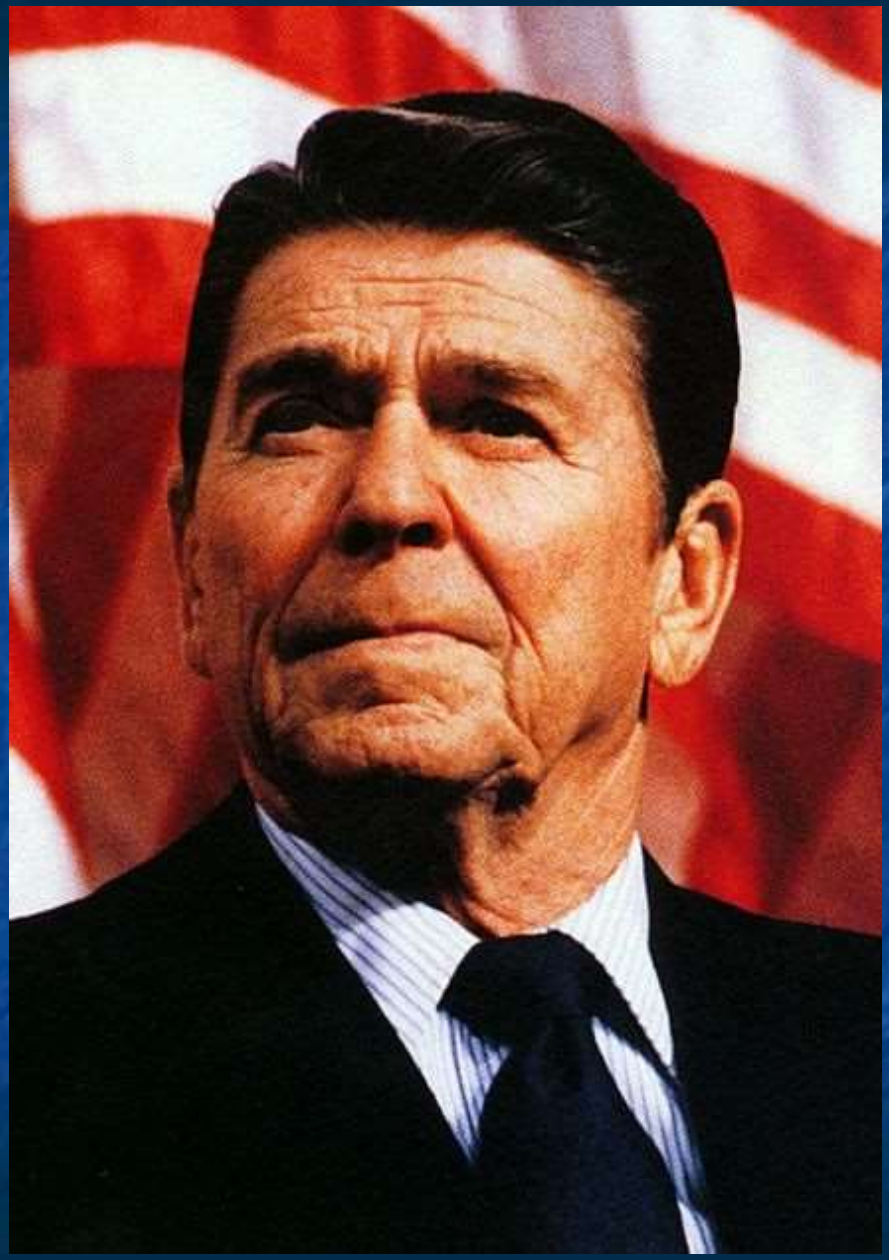
Father of Gospel Music

He wrote the gospel hit songs:
"Peace in the Valley" and
"Take my Hand, Precious Lord"



Rita Hayworth

Actor



Ronald Reagan

40th President of USA

Margaret Thatcher

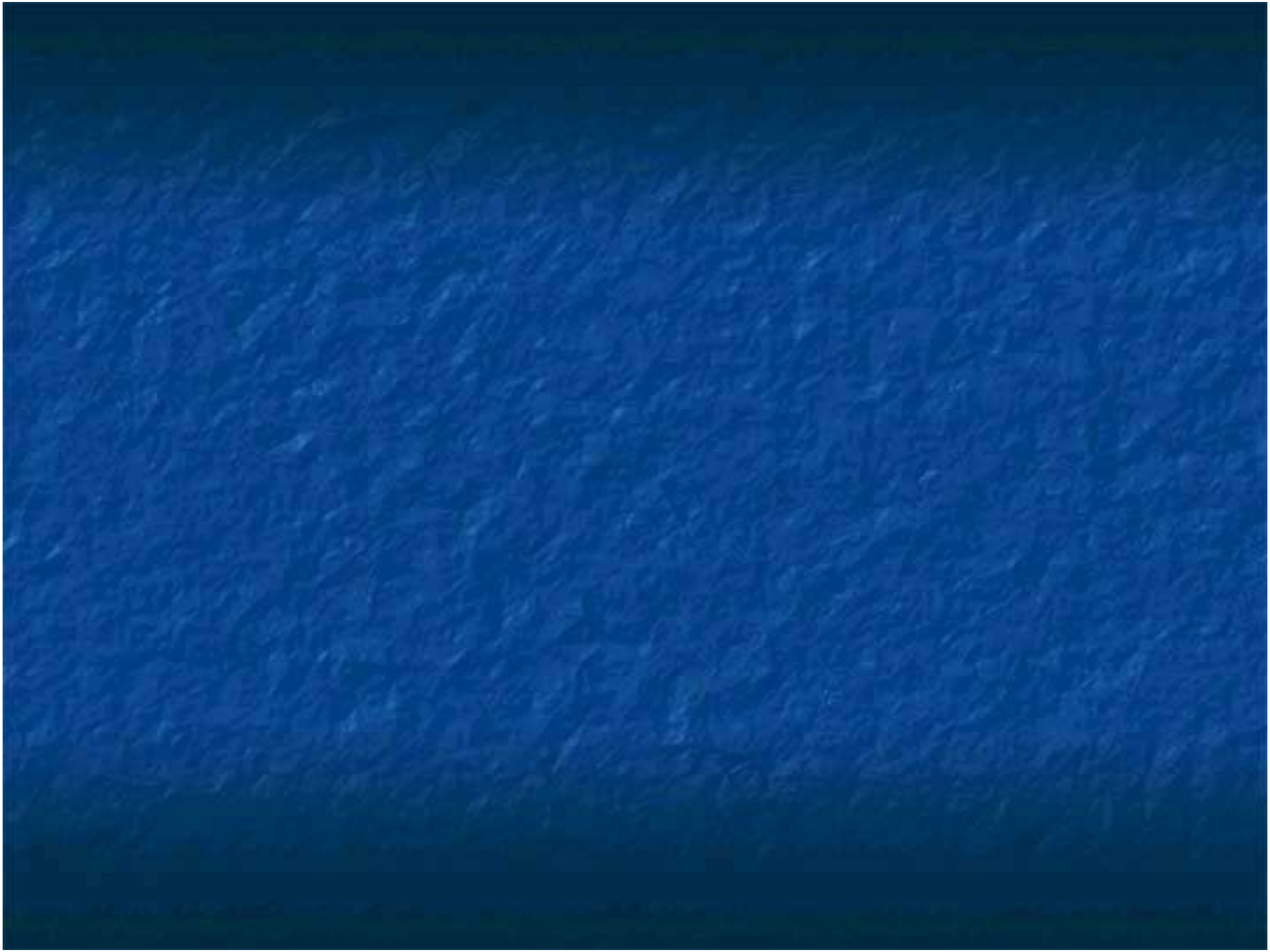
British Prime Minister

Harold Wilson

British Prime Minister

Oil Painting by Warner Zabel
(an Alzheimer's victim)

THANK YOU



June's is a large web site with a colorful home page and contains over 270 pages, articles and essays about every phase of Alzheimer's.

It has the most complete information about Alzheimer's anywhere on the Internet.

www.junebergalzheimers.com

Web Site Main Navigation

About June

- June and Marriage (Alzheimer's related)
- June's Life…pre and Alzheimer's
- June and Alzheimer's - in depth looks at June's Journey
- Tributes – Alzheimer's related
- In Memoriam – June and other Alzheimer's victims…
- Letters to the Children (during June's Alzheimer's years)
- Poems of June – with an Alzheimer's connection

Alzheimer's Information

- About Alzheimer's – all phases of Alzheimer's
- Care Practices – care of Alzheimer's victims
- Alzheimer's Drugs – includes diet items
- Funding – Alzheimer's Research
- Businesses that Help

www.junebergalzheimers.com

This presentation is dedicated to June K. Berg.

June married Stanton Berg in 1952 and became the love and light of his life. June has 4 children: David, Dan, Susan and Julie, 10 grandchildren and 10 great grandchildren. The 10th great grand child was a girl named “June” in honor of her grandmother.

When June was active, she enjoyed her family, friends, gathering collectibles, reading, dancing, travel, photography and church activities.

Her church activities over the years included: Girl Scout Leader, Sunday School Teacher, Church Board, Bell Choir, Nursing Home Volunteer, Women's Circles, Evangelism Team, "Meals on Wheels" and a "Bible Study Fellowship" participant.

June was diagnosed with Alzheimer's in January 1998 after noting short term memory problems in 1997. June was admitted to the Wellstead of Rogers, an Alzheimer's Assisted Living facility in 2005. In 2006 June was transferred to the "Alzheimer's wing" (Villa) of the Benedictine Health Care Center at Innsbruck. June passed away from complications of Alzheimer's on 23 October 2008 after an exhausting battle of almost 12 years.

During the last two years of June's life, she was largely non-responsive. June rarely opened her eyes. She did not talk and could not walk. It was difficult to feed her and she had problems with accepting food, drink or swallowing. As is typical of the late stages of this disease, June's life had very little or no quality.

Note: The Alzheimer's Unit had a 19 resident capacity. When June was admitted, there were 6 male residents in the "Villa." While there had been a turn over in male residents due to death, during the entire time of June's stay in the Alzheimer's Villa of the Benedictine, all the male residents were WWII veterans. One of the 13 female residents was also a WWII veteran. June was a long time member of Fridley American Legion Auxiliary Unit No. 303.

This presentation is also dedicated to Warner Zabel.

In 2006, Warner was diagnosed with Alzheimer's Disease.

Warner lived in Minnesota with his loving wife, Lucille. Warner had four sons: Bob, Jim, David and Mark who provided many grandchildren and one great-grandchild. Warner was a retired farmer and a veteran of World War II. He enjoyed fishing, playing cards and oil painting.

Warner died of complications of Alzheimer’s in September 2008 just a month before June also passed away from complications of Alzheimer’s.

PRODUCTION CREDITS:

Editor and Producer – Stanton O. Berg

Statistical Data – Much of the statistical data comes from the National Institute of Health, the National Center for Health Statistics and the Minnesota Department of Health as well as the Alzheimer's Association.

Funding Chart – This excellent chart is used courtesy of the AARP

Photos – Many of the photos in this presentation have been reproduced from the Administration on Aging web site. As a Federal government site, the material is in the public domain. Other photos that are in the public domain.

*** Note: The original creator/producer of Edition 1, and the co-editor and producer of Editions 2 through 5, was Patti J. Paulson**

*** Current edition: 11th Edition - 2013**

WE'D LIKE TO HEAR FROM YOU

Please send your comments, suggestions or feedback to:

Email: stan@junebergalzheimers.com