Temi del libro

- **Differenza** fra il *normale* indebolimento cognitivo in età avanzata e la demenza
- **Evitare** procedure diagnostiche inutili, psicologicamente pesanti ed eticamente dubbie.
- **Ridurre** il rischio della demenza
- Problemi **etici**

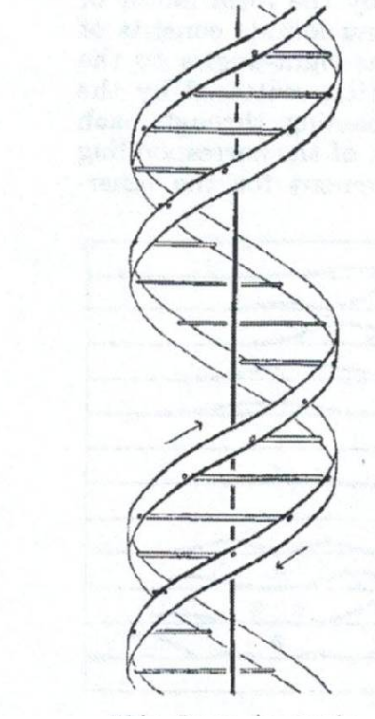
2018

Roger Bacon
(1214-1294)

Differenza fra il *normale* indebolimento cognitivo in età avanzata e la demenza

„L‘età avanzata è il tempo della dimenticanza.“

F. Crick, J. Watson 1953



Perché e come invecchiamo

Neurobiology of Aging
53,36-47,2017
I geni dei mitocondri sono prematuramente alterati nelle malattie neurodegenerative e quindi nell'AD

stabilisce l'età genetica

misure preventive sociali e personali

età epigentica invecchiamento

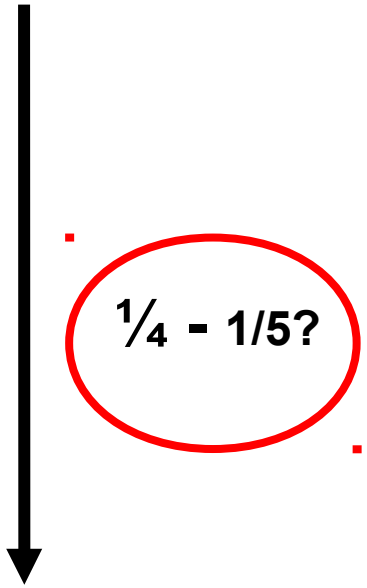
Senescenza

- Deterioramento psicofisico dell'età avanzata
- I meccanismi cognitivi (in particolare memoria e concentrazione) diventano meno efficienti.

- **Non è demenza, nemmeno iniziale**

Senescenza: ***rallentamento***

dei processi cognitivi,
a partire dalla memoria



mente intatta

Demenza: ***distruzione***

progressiva dei mec-
canismi nervosi della
mente

Stadi della senescenza mentale

B. Reisberg *Amer. J.Psychiat. 139, 1136-1139, 1982*

- **Stadio 1: Indebolimento cognitivo dopo i 65 anni [„*smemoratezza senescente benigna*“]**

- **Stadio 2: Blando deterioramento cognitivo MCI (mild cognitive impairment) o CIND (*cognitive impairment no dementia*)**

NON SONO DEMENZE

¼ ?

diventa demente

MCI
mild cognitive impairment

Mayo Clinic 1999

Arch. Neurol. 56,303-308,1999

Neurology 56, 1133-1142,2001

- ***15-20%*** ***oltre i 65 anni***
- **Indebolimento della memoria episodica e semantica,** ***superiore alla media dell'età***
- **Comportamento normale**
- **Funzioni cognitive normali**
- **Miglioramenti spontanei (1/4?)**
- ***Possibile*** ***transizione fra invecchiamento normale e patologico con rischio di demenza***
- **1/4 (?) diventa demente**

Acta Psychiat. Scandinav. 119, 252-265,2009

„Passaggio annuale da MCI a AD 5-10%. La maggioranza della popolazione non diventa demente nei 10 anni successivi alla diagnosi di MCI.“

MCI : 1/4 migliora ?
(*Alzheimer Disease & Ass. Disor. (30,324-330,2016)*)

Metanalisi di 25 studi, età 70-79 anni. Durata: 1-17 anni

Migliorati fino alla normalità: 24% (2% ➔ 59%)

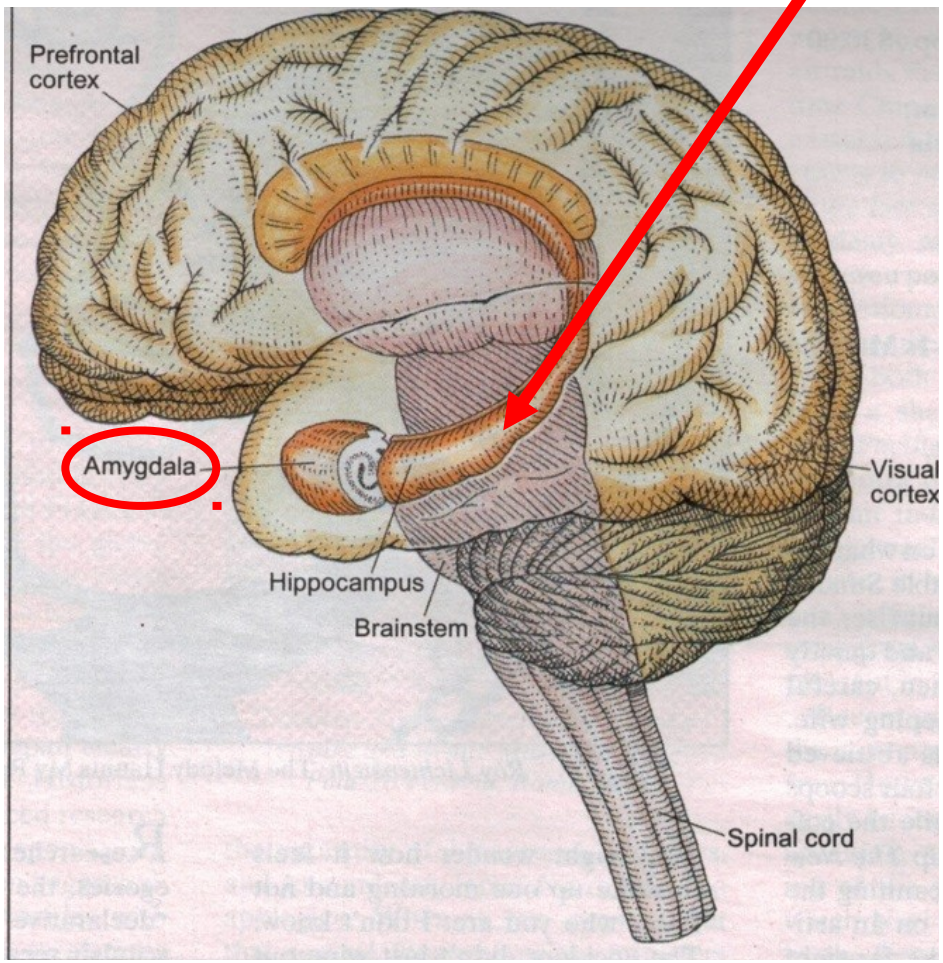
Stadi della demenza

B. Reisberg *Amer. J.Psychiat. 139, 1136-1139, 1982*

- **Stadio A : Blanda demenza (difficoltà del-l'orient. spaziale, difficoltà quotidiane, aprassia, appiattimento degli affetti) 2-3 anni**
- **Stadio B: Moderata demenza (memoria quasi sparita) 1-2 anni**
- **Stadio C: Severa demenza (incapace delle incombenze più semplici) 2-3 anni**
- **Stadio D: Grave demenza**

Demenza

Ippocampo organo della memoria e dell‘affettività (sistema limbico)



- **Debolezza della memoria, fino alla scomparsa**
- **Imbarazzo, vergogna, insoff-erenza, depressione**
- **Attacchi di panico, accuse, senso di persecuzione, pianti, lamenti, disperazione**
- **Agitazione**
- **Insonnia e altri disturbi del sonno**
- **Allucinazioni drammatiche**
- **Disturbi del linguaggio, della visione, della marcia, del senso del tempo**
- **Momenti d‘autocoscienza**

Demenza

- **Ammalati nel mondo: 33.9 milioni nel 2011, 47 milioni nel 2016 90% oltre 65a**

- **Il prolungamento dell'attesa di vita di 6 anni e 3 mesi raddoppia il numero dei dementi senili.**

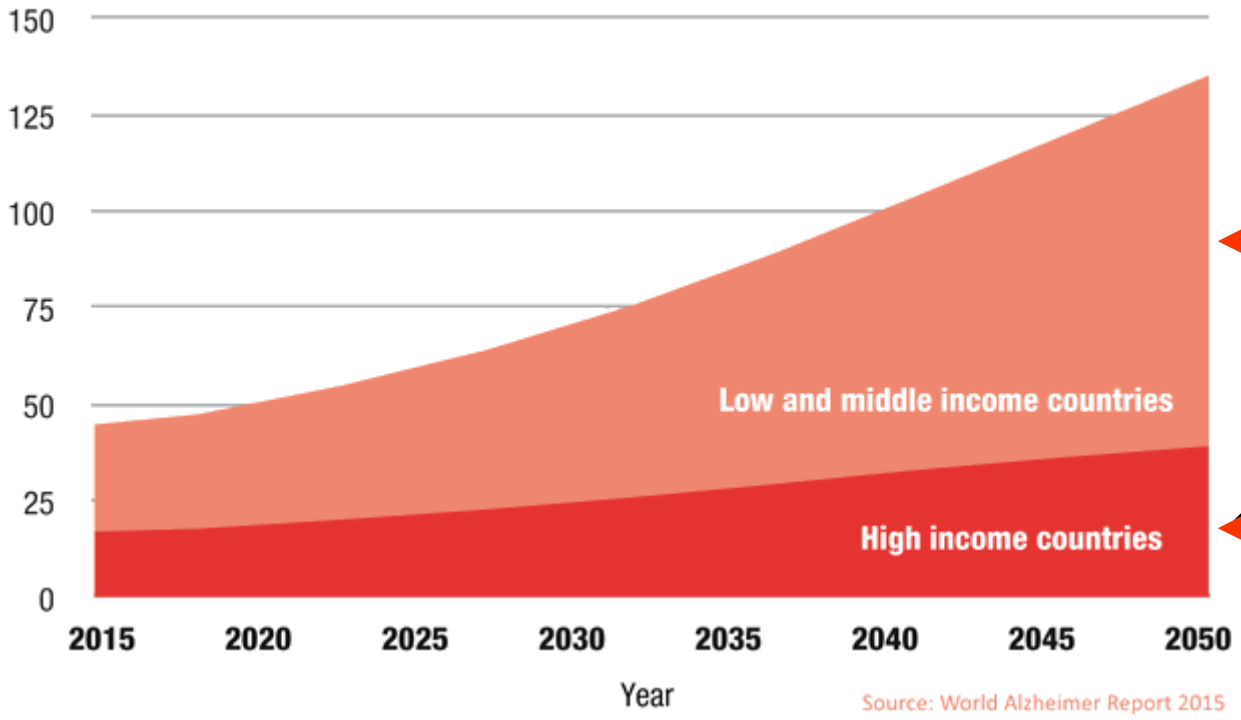
- **Negli ultimi 20 anni incidenza stabile o regrediente (California, UK, Svezia, ecc)**

- **Cresce molto in Cina e Giappone**

*** „** ***L'aumento della durata della vita rende la fragilità mentale una delle più gravi minacce all'umanità del XXI secolo.“***
Nature 464, 529-535,2010

Presumibile numero di dementi dal 2015 al 2050 in paesi con reddito medio-basso e reddito alto

Milioni di dementi



Reddito medio-basso

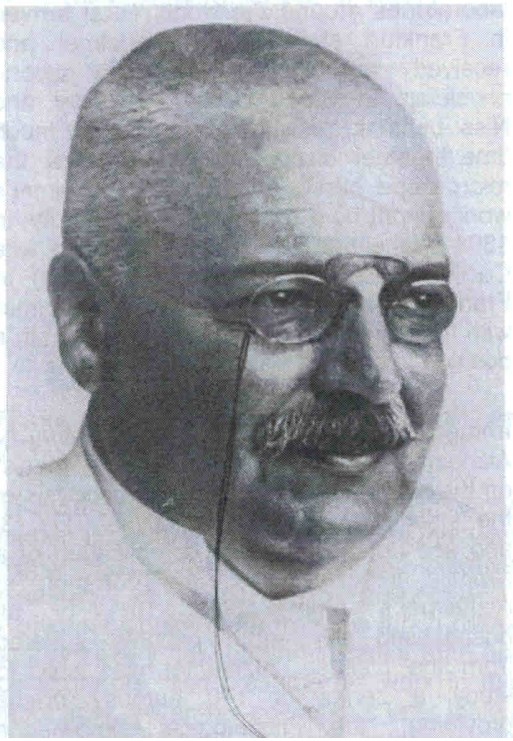
Reddito alto

Italia (2015) 1.300.000

World Alzheimer Report 2015

Zeitschrift für gesam. Neurolog. u. Psychiat. 4,356-385,1911

Alois Alzheimer 1864-1915



„Dobbiamo concludere che le placche non sono la causa della demenza senile, ma solo una manifestazione accessoria dell'involuzione senile del sistema nervoso."

- **Placche (amiloidi) nei lobi parietali e temporali**
- **Casi di demenza senile grave con poche placche o senza placche**
- **Degenerazione neurofibrillare (tau) non costante, anche con molte placche**
- **Clinica: agnosia, aprassia, afasia. Più grave che nelle demenze senili**

•**Evitare** procedure diagnostiche inutili, psicologicamente pesanti ed etica-mente dubbie.

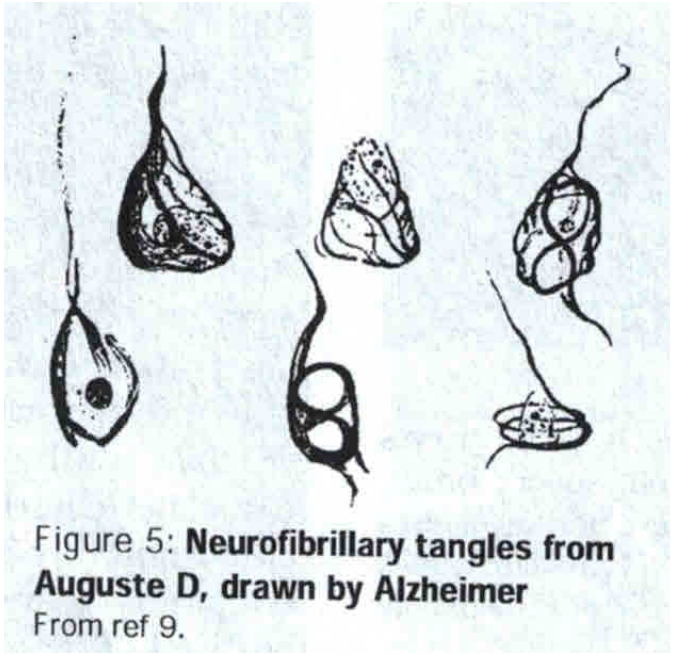
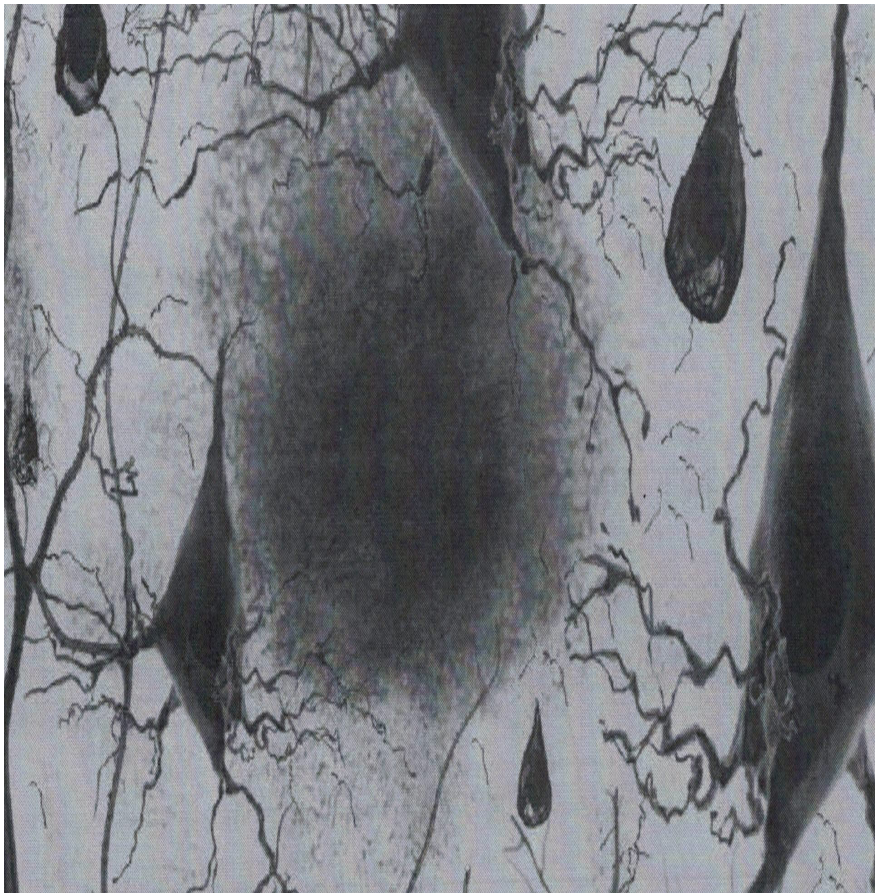
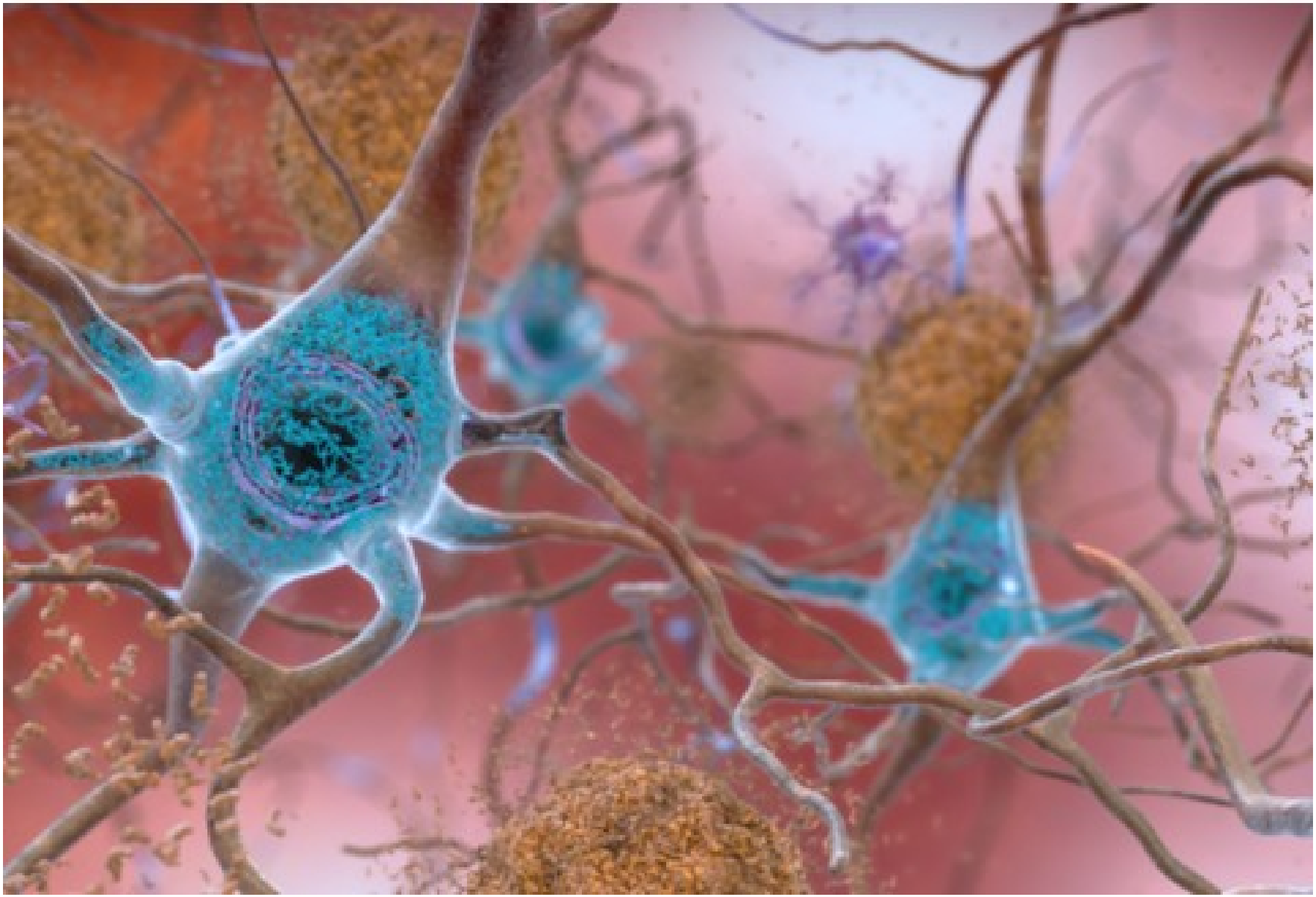


Figure 5: **Neurofibrillary tangles from Auguste D, drawn by Alzheimer**
From ref 9.

Neurofibrille nelle cellule nervose



Placche amiloidi fra i neuroni



Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

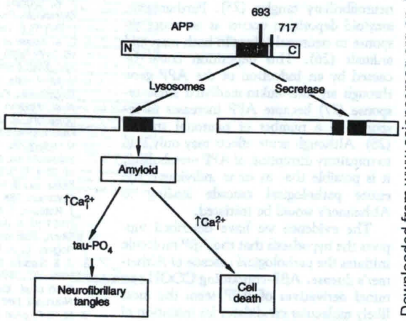
Alzheimer's disease causes dementia in many elderly people and in some individuals with Down syndrome who survive to age 50. Alzheimer's is characterized by various pathological markers in the brain—large numbers of amyloid plaques surrounded by neurons containing neurofibrillary tangles (*1*), vascular damage from extensive plaque deposition (*2*), and neuronal cell loss (*1*). Because it is not known if the amyloid plaques or the neurofibrillary tangles are the earliest lesion in the disease process, the role of these markers in the etiology of the disease is controversial.

Our hypothesis is that deposition of amyloid β protein (AβP), the main component of the (*3*) plaques, is the causative agent of Alzheimer's pathology and that the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition. AβP is a peptide product of the larger amyloid precursor protein (APP) (*4*). Because Down syndrome is caused by trisomy of the region of chromosome 21 that contains the APP gene, deposition of AβP is likely to be an early event in the disease (*5*). The AβP molecule is a 39– to 42–amino acid peptide (*4, 6*), part of which forms the hydrophobic transmembrane domain in the COOH-terminal portion of APP (Fig. 1). AβP is one of a diverse group of "amyloid" (starch-like) proteins that forms insoluble extracellular deposits. The APP gene undergoes alternative RNA splicing to produce several protein isoforms; the predominant variant in brain lacks a serine protease inhibitor domain that is present in APP molecules in other tissues (*7*).

We now know something about how APP proteolysis leads to AβP deposition. APP is inserted into the cytoplasmic membrane and then cleaved at residues 15 to 17 within the AβP sequence by the APP "secretase" (*8*) (Fig. 1). This cleavage event therefore produces fragments that do not contain intact AβP and so cannot result in amyloid deposition. These fragments include secreted NH_2-terminal derivatives that can be detected in brain and cerebrospinal fluid (*9*). The APP secretase that cuts within the AβP region has an extraordinarily broad sequence specificity and recognizes the secondary structure of APP, cleaving at a defined distance from the membrane (*10*). Several recent studies suggest that APP can also be processed by the endosomal-lysosomal pathway, after recycling of membrane-bound APP and possibly via an intracellular metabolic route (*11–13*). Carboxyl-terminal fragments containing the entire AβP sequence can be derived from this alternate normal processing of APP (*12, 14*) and may eventually lead to amyloid deposition (*12, 14*) (Fig. 1).

J. A. Hardy, Department of Biochemistry, St. Mary's Hospital Medical School, London W2 1PG, U.K., and Department of Psychiatry, University of South Florida, Tampa, FL 33612.
G. A. Higgins, Molecular Neurobiology, Laboratory of Biological Chemistry, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224.

Fig. 1. The amyloid cascade hypothesis. Processing of APP can occur via two pathways: (i) Cleavage within AβP by the secretase, which generates peptide products that do not precipitate to form amyloid and (ii) cleavage in the endosomal-lysosomal compartment, resulting in intact AβP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer's disease.

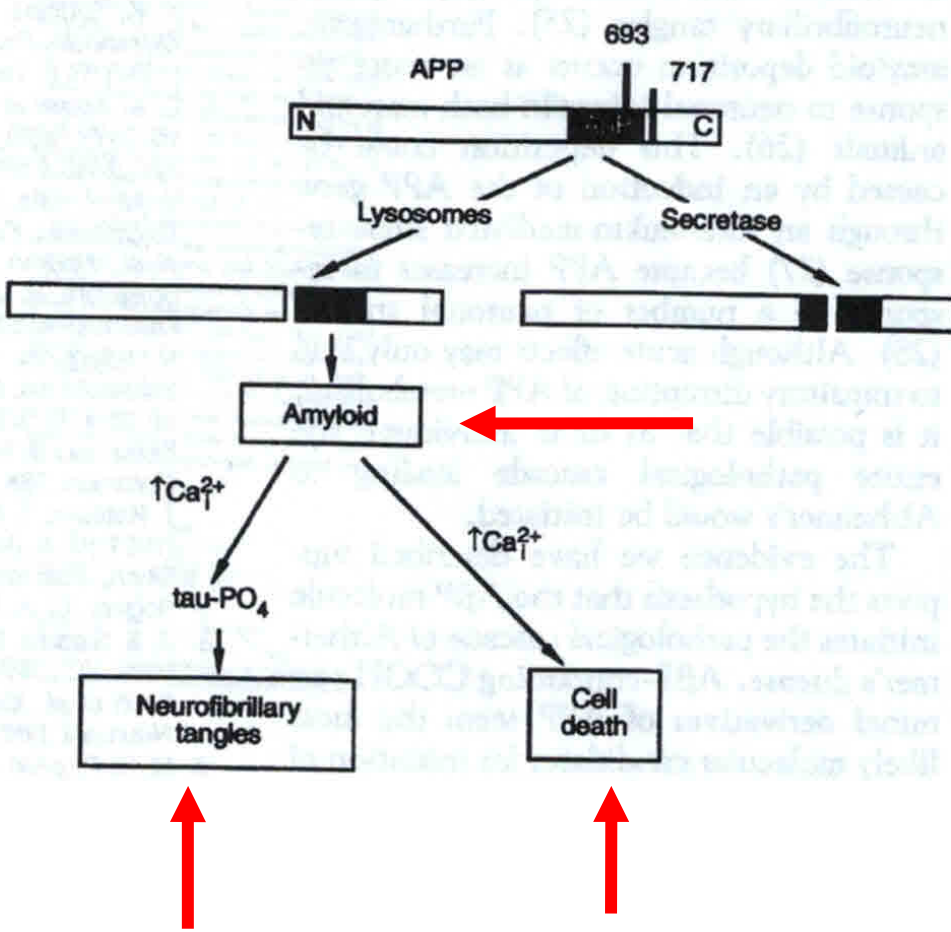


Mutations in the COOH-terminal portion of APP cause hereditary, early onset Alzheimer's disease (*15, 16*) and hereditary cerebral hemorrhage with amyloidosis (Dutch-type) (*17*). The APP mutation that causes massive AβP deposition in the Dutch amyloidopathy is a glutamic acid to glutamine substitution at codon 693 [with reference to the longest form of APP, APP-770 (*7*)] (Fig. 1), located only six residues away from the cleavage site within the AβP sequence (*17*). It has been speculated that this mutation might cause AβP deposition by inhibiting secretase cleavage of APP, although this now seems less likely because of the apparent lack of sequence specificity of the enzyme (*10*).

Three mutations have been described within the APP gene that cause familial Alzheimer's disease. These mutations all occur at codon 717 of the protein (*15, 16*) and change the native valine, located three residues from the COOH-terminal end of AβP, to isoleucine, phenylalanine, or glycine (Fig. 1). It is unclear how these mutations cause amyloid deposition, but they may inhibit the breakdown of a COOH-terminal fragment of APP that contains AβP (*15*), alter the anchoring of APP in the cell membrane, or stabilize AβP-containing amyloidogenic fragments within lysosomes (*12, 15*).

Our cascade hypothesis states that AβP itself, or APP cleavage products containing AβP, are neurotoxic and lead to neurofibrillary tangle formation and cell death. Thus, two successive events are needed to produce Alzheimer's pathology. First, AβP must be generated as an intact entity, either by accumulation of AβP or as an AβP-containing fragment of APP. Second, this molecule must facilitate or cause neuronal death and neurofibrillary tangle formation. Neve and her colleagues have reported that the AβP-containing COOH-terminal fragment is toxic to cultured neurons (*18*), and Kowall and co-workers (*19*) have suggested that AβP alone exerts toxic effects on neurons, an effect possibly mediated through the serpin receptor (*20*). Other investigators, however, have reported that AβP itself is not neurotoxic, but that it renders neurons more sensitive to excitotoxic damage (*21*). Although it is not clear exactly how AβP causes neuronal loss and tangle formation, the peptide is known to disrupt calcium homeostasis and increase intraneuronal calcium concentrations (Fig. 1). This observation could explain how neurofibrillary tangles form. The tangles are largely composed of paired helical filaments formed from a hyperphosphorylated form of the microtubule associated protein, tau (*6*),

Science 256, 184-185, 1992



The Gerontologist
Vol. 37, No. 2, 150–156

Sister Mary, the gold standard for the Nun Study, was a remarkable woman who had high cognitive test scores before her death at 101 years of age. What is more remarkable is that she maintained this high status despite having abundant neurofibrillary tangles and senile plaques, the classic lesions of Alzheimer's disease. Findings from Sister Mary and all 678 participants in the Nun Study may provide unique clues about the etiology of aging and Alzheimer's disease, exemplify what is possible in old age, and show how the clinical expression of some diseases may be averted.

Key Words: Neuropathology, Alzheimer's disease, Dementia, Cognition

Aging and Alzheimer's Disease: Lessons From the Nun Study[1]

David A. Snowdon, PhD[2]
Center of Aging Kentucky

„*Sister* Mary era una donna con notevoli capacità cognitive fino alla fine della vita a 101 anni. Ciononostante, all'autopsia si trovarono neurofibrille e placche in gran quantità. Lei e altri 678 partecipanti allo studio dimostrano che l'espressione clinica di alcune malattie può mancare."

Persone anziane (anche novantenni e oltre) senza demenza hanno le alterazioni cerebrali attribuite all'AD (amiloidi, tau).

Neurology 66, 1841-1844, 2006

British medical J. 341, 2010https://doi.org/10.1136/bmj

- **Non c'è rapporto costante fra la clinica dell'AD e le caratteristiche anatomopatologiche (tau, placche) attribuite all'AD.**

- **„Alzheimer senza Alzheimer"?**
- **„Alzheimer precoce"?**
- **„Diagnosi precoce"?**

- **„La maggioranza delle persone attualmente con alterazioni dell'AD (amiloidosi, tau o entrambe) SONO PRECLINICHE" [CIOÉ SONO SANE]**

  Alzheimer's & Dementia 14, 121-129, 2018

„Il campo dell'Alzheimer è oggi stracolmo di controversie circa incertezze, cose ignote, tentativi falliti, insufficienze dei modelli animali." **Margaret Lock N.Y.R.of Books July 10 2014**

„ La maggioranza delle persone con AD preclinica NON AMMALERÀ DI DEMENZA “ [46.7 milioni di persone]

***„La presenza della AD preclica NON SIGNIFICA necessariamente un‘alta probabilità di* ammalare di demenza.“** **Alzheimer‘s & Dementia 14, 981-988,2018**

„Una parte sostanziale di pazienti dementi non avevano avuto i cosidetti prodromi della malattia di Alzheimer.“ **Brain 138, 1327-1338,2018**

Current Biology
28, R635-R655,2018

- *„Nonostante qualche successo nella rimozione delle placche, non si é mai avuto un beneficio, … perché non c'è stato nessun miglioramento marcato delle funzioni cognitive."*

- *„… non esiste alcun trattamento della AD…un ritardo dell'insorgenza della malattia può essere raggiunto spesso con una semplice modificazione dello stile di vita."*

Alzheimer's & Dementia
14, 1383-1385, 2018

- Biogen & Eisai: BAN2401/Placebo
- 800 pazienti con MCI o AD iniziale
- 5X iniezioni endovena 10mg/kg 2 volte per settimana
- Nel gruppo BAN2401 regressione delle placche amiloidi del 93%
- Nessuna efficacia cognitiva
- Rallentamento del declino cognitivo?

Biogen halts studies of closely watched Alzheimer's drug, a blow to hopes for new treatment

By Adam Feuerstein @adamfeuerstein

March 21, 2019

Biogen abandons Alzheimer's drug

Treatment withdrawn from trials • Shares slide 30% • Cure elusive despite investment

PETER WELLS — NEW YORK
HANNAH KUCHLER — SAN FRANCISCO

Biogen and its Japanese partner Eisai are to abandon trials of their Alzheimer's treatment, dealing a blow to efforts to defeat the disease and sending the US drugmaker's shares down almost 30 per cent.

The companies said yesterday that they had decided to discontinue global Phase III trials of aducanumab after a "futility analysis", conducted by an independent monitoring committee, indicated the drug was not going to prove effective.

The disappointment adds aducanumab to a list of once-promising Alzheimer's drugs that have failed in the late stages of testing, leaving the industry with little to show for billions of dollars of investment.

Aducanumab was being tested on Alzheimer's patients with mild cognitive impairment and mild dementia. Biogen and Eisai said the recommendation to stop the studies was not based on safety concerns. "This disappointing news confirms the complexity of treating Alzheimer's disease and the need to further advance knowledge in neuroscience," said Michel Vounatsos, Biogen chief executive.

Biogen shares were down 28 per cent in early afternoon trading, wiping about $18bn from its market value, which stood slightly above $63bn at the close on Wednesday. That sent the stock to its lowest level since mid-2016.

The Alzheimer's treatment was Biogen's single most significant prospect in a pipeline of drugs that investors hoped would secure the company's future. Its existing products face intensifying competition, with its multiple sclerosis treatment challenged by Genentech and its muscular dystrophy drug expected to have a rival from PTC Therapeutics.

Tom Shrader, biotech analyst at BTIG, cut his rating on Biogen from "buy" to "neutral" after the aducanumab failure but said the drugmaker was "still an aggressive company with a knack for finding new directions".

> Outcome 'confirms complexity of treating Alzheimer's disease'
>
> Michel Vounatsos, Biogen chief

Favourable results for aducanumab in Phase II studies last year appeared to validate the amyloid hypothesis, which proposes that memory loss and other Alzheimer's impairments are due to build-up of sticky plaques in the brain.

Support for the hypothesis has fallen in recent years after drugs from Merck & Co, Eli Lilly and AstraZeneca, stumbled in final Phase III trials.

Jim Kupiec of ProMIS Neurosciences said targeting plaque had been proven to be the wrong tactic and that an approach focused on proteins in the brain was showing promise.

Financial Times 22.03.19

Neurobiology of Aging 77,26-36, 2019

- 161 persone sane di mente fino al decesso
- Età alla visita: 62-100 anni (media 87)
- Età al decesso: 62-103
- Autopsia (1999-2015):
- B-Amiloidi : 57 % (49% forte, 13% molto forte)
- TAU: in tutte tranne 4
- Lesioni vas.: (microinfarti e infar.) 45%

Acta Neuropathologica (2018) 136:663–689
https://doi.org/10.1007/s00401-018-1918-8

REVIEW

CrossMark

Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease

Gary P. Morris[1,2] · Ian A. Clark[3] · Bryce Vissel[1,2]

Domande circa il ruolo della beta-amil. nella definizione, nelle cause e nella diagnosi dell'AD.

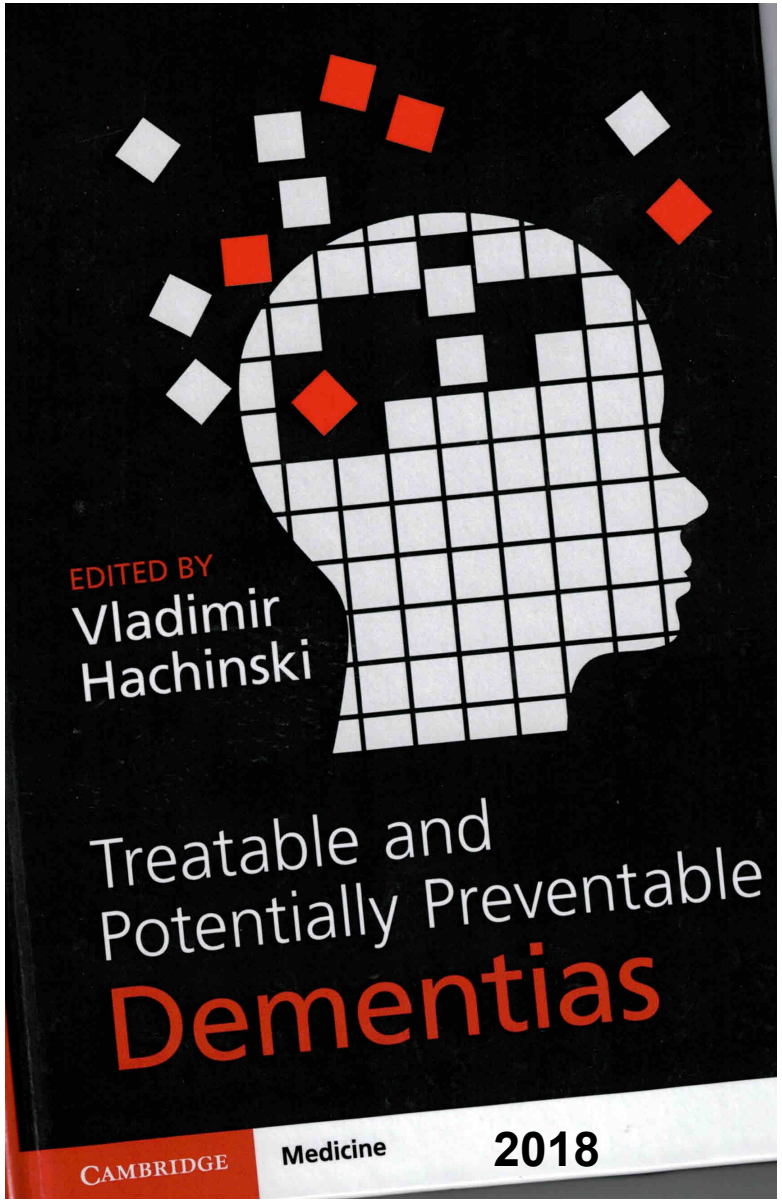
1.- Nella persona normale dal punto di vista cognitivo ci possono essere beta-amil. e tau? SI
2.- Ci sono individui con la diagnosi clinica di AD senza beta-amil.

e tau? SI
3.-Le dimensoni e l'eventuale progressione delle placche amil. sono correlate alla progressione del declino cognitivo? NO
4.-La comparsa delle amil. é il primo segno biologico della demenza? NO

Ridurre il rischio della demenza

Alzheimer‘s & Dementia
14,845-847, 2018

- **„Quasi tutti i tentativi di trovare prevenzioni e trattamenti efficaci della demenza sono *falliti*…*L‘unica strada per ridurre il gravame della demenza è l‘intervento sullo stile di vita.“***



„Most Alzheimer pathology (plaques and tangles) occur silently without resulting in cognitive impaiment.“

„La maggior parte della patologia dell‘Alzheimer (placche e tau) si sviluppa inavvertitamente senza disturbi cognitivi.“

Inizia una nuova era

A New Era Begins

Vascular lesions, Alzheimer lesions, and Lewy bodies are common in elderly individuals; however, it is multiple pathologies that increase the risk of developing cognitive impairment.[79] In a large autopsy series of 6,205 patients, it was established that all major dementias have a vascular component, ranging from 60 percent frontotemporal dementias to 80 percent in Alzheimer disease(Figure 1.11).[71] It seems that having a vascular component can double the chance that neurodegenerative pathologies will result in dementia. In fact, the largest component of cognitive impairment can be explained by vascular and/or

Demenza/Incidenze annuali

- ***Advances in Gerontology 16, 30-37,2005***

  1999: USA 310.000 casi di demenza oltre i 65 anni meno che nel 1982

  (5,7➔2.9% della popol.)

- ***Nature Communications 7, 11398,2016***

  In UK nel 2015: 210.00 nuovi casi di AD anziché 250.00 (2014)

stabilisce l'età genetica

Neurobiology of Aging
53,36-47,2017
I geni dei mitocondri sono prematuramente alterati nelle malattie degenerative e nell' AD

Alzheimer's & Dementia
14,1099,2018
„… Il danno del DNA è la forza pato-genetica determinante della neurode-generazione e del declino cognitivo."

età epigenetica
invecchiamento

misure preventive
sociali e personali

„La causa della AD è probabilmente multifattoriale, e consiste di un cocktail di fattori ambientali e genetici e dello stile di vita." **Curr. Biol. 28, R635-655, 2018**

„Il modello concettuale di demenza è di considerare la AD una *sindrome* piut-tosto che una malattia" Alz.& Dem.Translational Res.a Clin.Invest. 3, 571-578, 2017

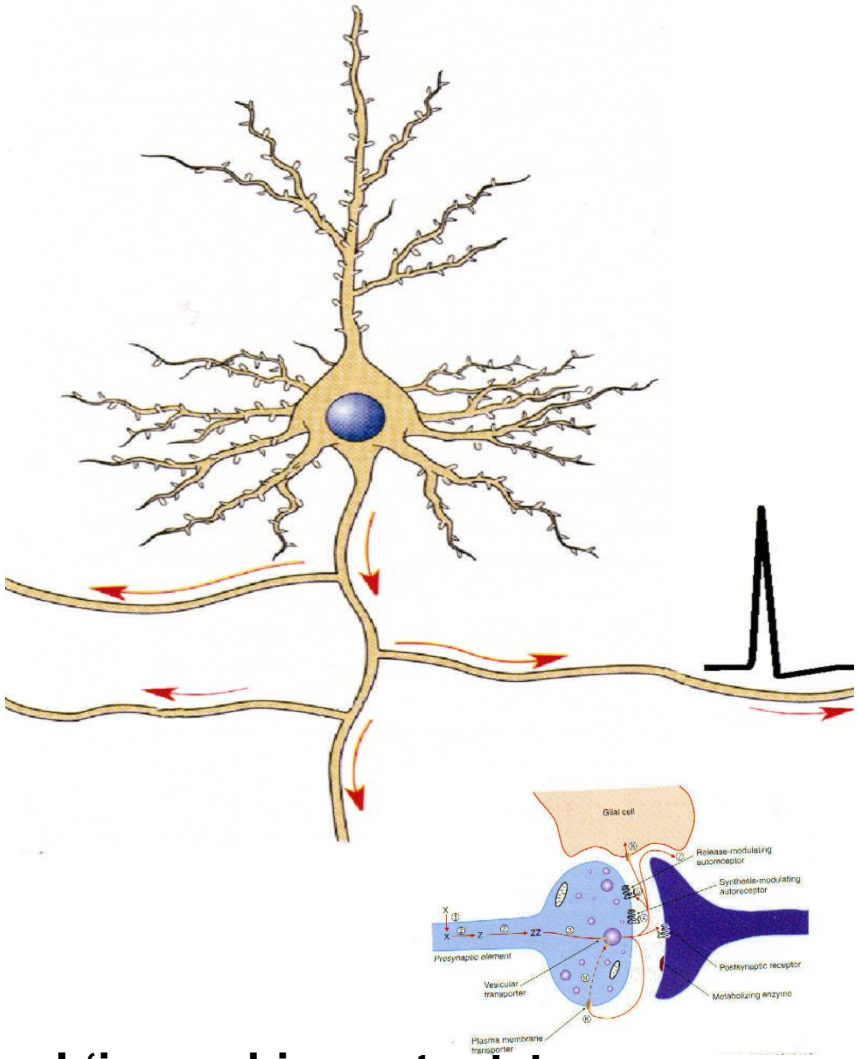
Demenza

- La demenza è, nella maggior parte dei casi, un evento gene-tico condizionato da fattori epigenetici.

- La demenza non è una malattia, ma una *sindrome* dovuta a più di una causa.

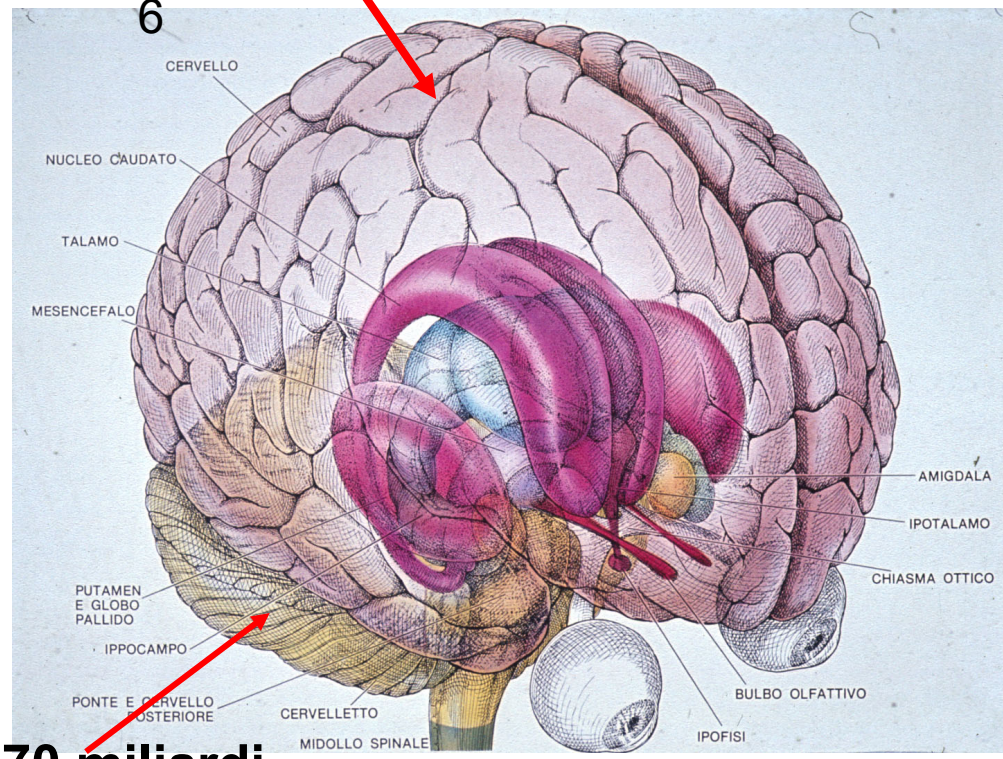
- Non c'è terapia, solo preven-zione generica e misure pallia-tive.

86 miliardi di neuroni



16 miliardi

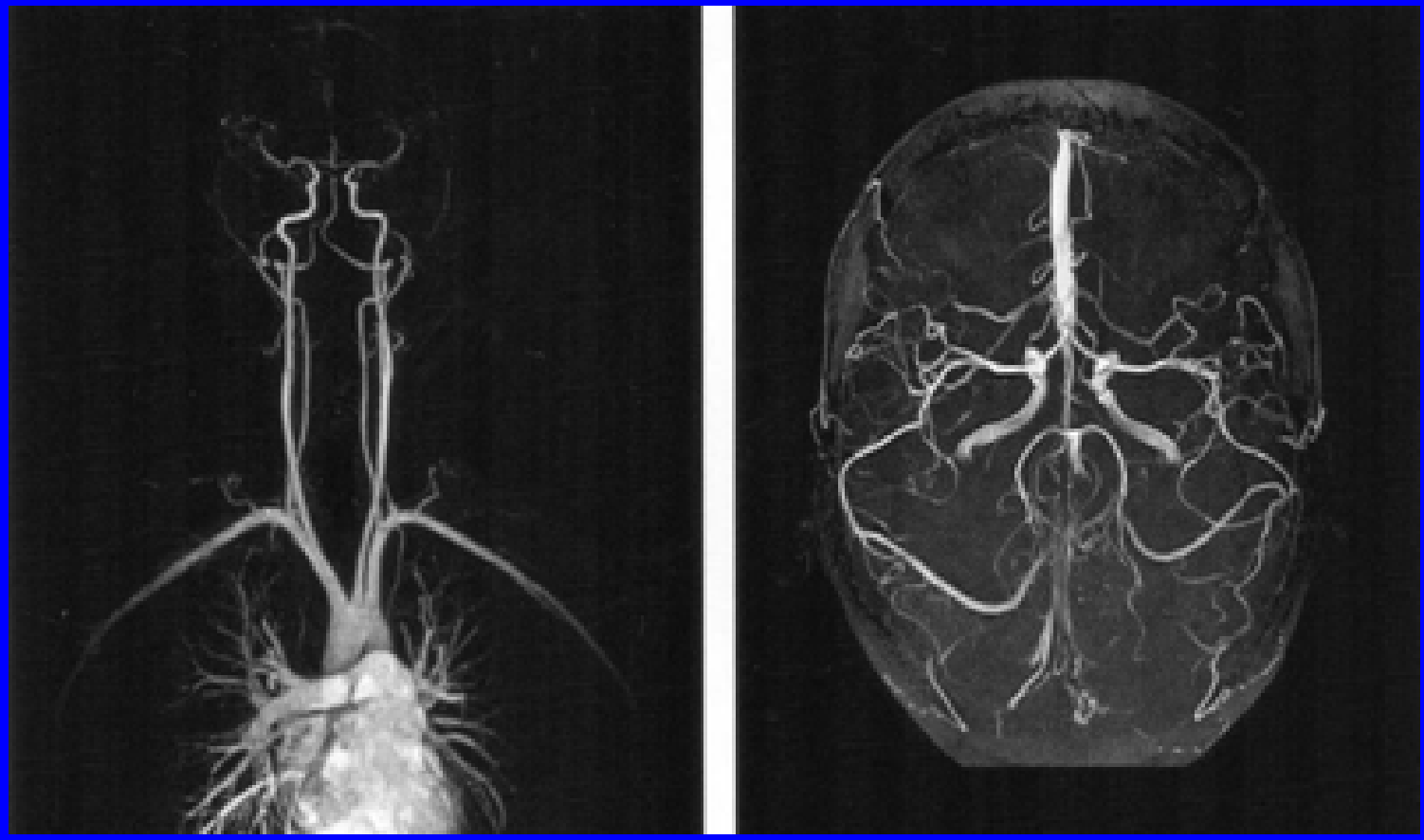
1
6



70 miliardi

L‘invecchiamento del cervello comincia a 24-25 anni

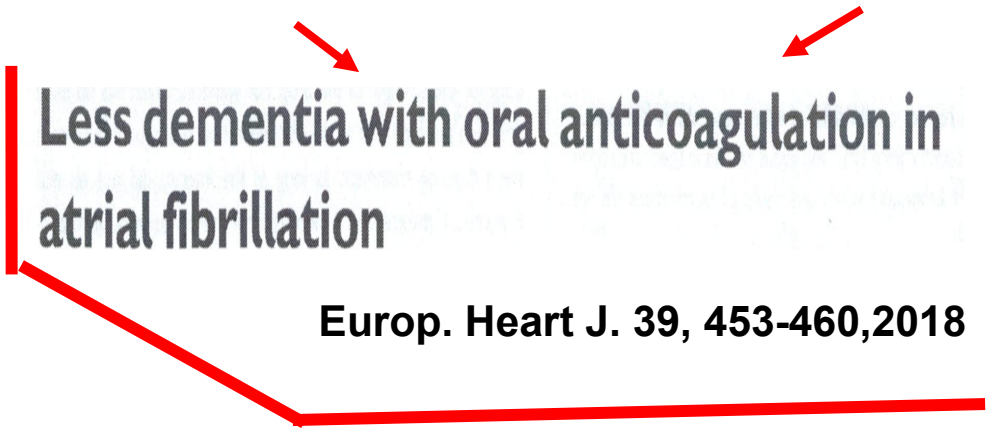
MRA



WHO 29.05.2017
Prevenzione della demenza come assoluta priorità della politica sanitaria

- *Fattori di rischio*

- **Disturbi cardiovascolari, in particolare ipertensione arteriosa e fibrillazione atriale**
- **Obesità**
- **Diabete**
- **Fumare**
- **Ridotta attività fisica**
- **Insonnia**
- **Basso livello culturale**
- **Depressione**
- **Riduzione dell'udito**
- **Alcolismo**



Europ. Heart J. 39, 453-460,2018

Lancet Neurol. 16,677,2017

- **„Sebbene al momento non si cono-scano interventi di prevenzione specifica… *l‘impegno cognitivo, l‘aumento dell‘attività fisica, il controllo scrupoloso della pressione sanguigna* possono essere misure preventive benefiche, anche se manca l‘evidenza scientifica definitiva.“**

Alzheimer‘s & Dementia 14, 121-129, 2018

- **Quasi 47 milioni di americani hanno placche e tau**
- **1/3 dei pazienti con AD ha un fattore di rischio (ipertensione,diabete)**
- ***Decisioni sulla base di segni, sintomi, e valori ematici, non di dati paraclinici**

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Alzheimer's & Dementia

Perspective

The clinical practice of risk reduction for Alzheimer's disease: A precision medicine approach

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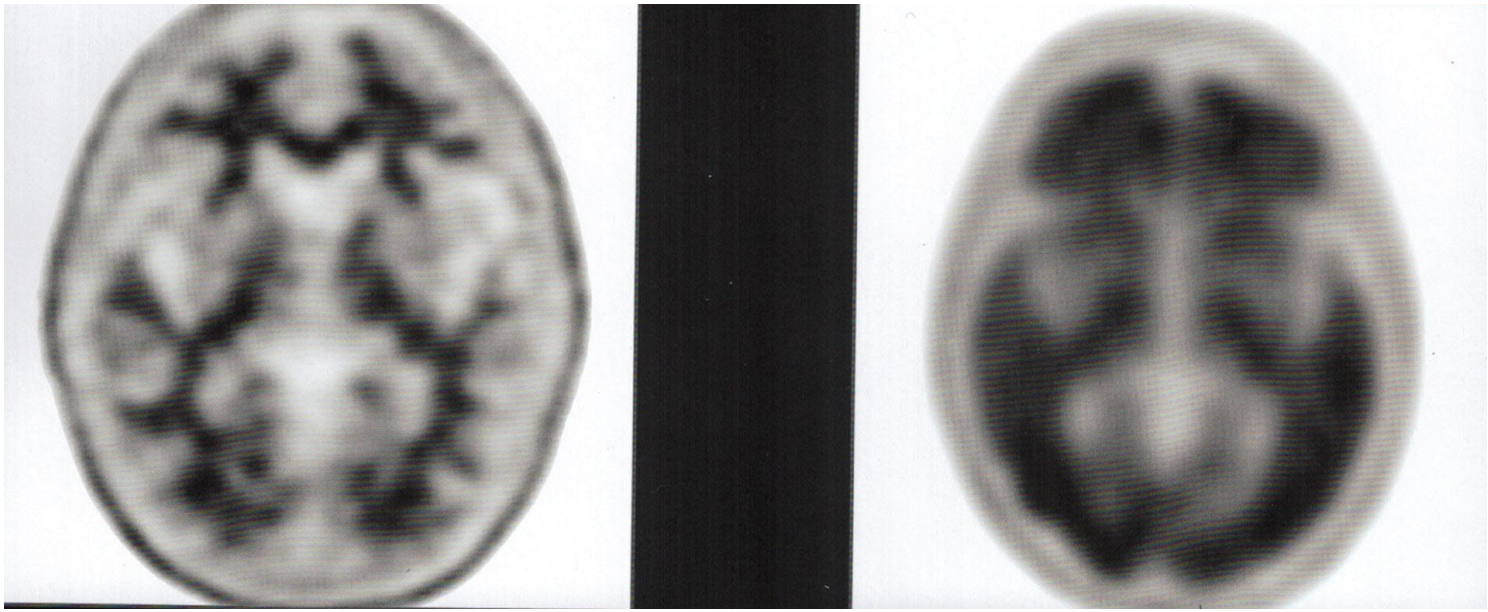
Abstract

Like virtually all age-related chronic diseases, late-onset Alzheimer's disease (AD) develops over an extended preclinical period and is associated with modifiable lifestyle and environmental factors. We hypothesize that multimodal interventions that address many risk factors simultaneously and are individually tailored to patients may help reduce AD risk. We describe a novel clinical methodology used to evaluate and treat patients at two Alzheimer's Prevention Clinics. The framework applies evidence-based principles of clinical precision medicine to tailor individualized recommendations, follow patients longitudinally to continually refine the interventions, and evaluate N-of-1 effectiveness (trial registered at ClinicalTrials.gov NCT03687710). Prior preliminary results suggest that the clinical practice of AD risk reduction is feasible, with measurable improvements in cognition and biomarkers of AD risk. We propose using these early findings as a foundation to evaluate the comparative effectiveness of personalized risk management within an international network of clinician researchers in a cohort study possibly leading to a randomized controlled trial.

Keywords: Alzheimer's disease prevention; Clinical precision medicine; Alzheimer's precision medicine; Multidomain interventions; Alzheimer's Prevention Clinic; Personalized medicine; APOE; Preclinical Alzheimer's disease

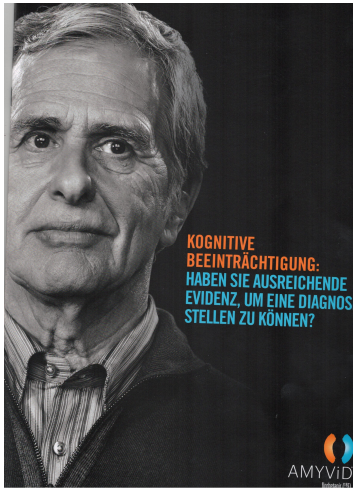
Problemi etici della demenza

- Informare l‘ammalato?
- A seconda delle circostanze personali e familiari
- Solo dopo l‘evidenza clinica, mai con indagini strumentali
- Mai diagnosi cosidette precoci in persone sane o con MCI. Non sono diagnosi, non aiutano e provocano solo angoscia.
- Fine vita



normale

AD, forse (?)



Amyvid Lilly 2016

„Non sufficiente per una diagnosi sicura di AD o di altri disturbi cognitivi, perché questi reperti possono trovarsi in pazienti anziani senza disturbi.“

Che fare?

- *„To care when there is no cure“*
- *To „live well/live better with dementia“*
- *Principio: lasciar vivere la persona come il cervello malato la fa essere, senza ferirne la dignità.*
- ***Misure palliative** in famiglia e negli ospizi*

La reazione all'aumento del gravame della demenza deve essere più rapido

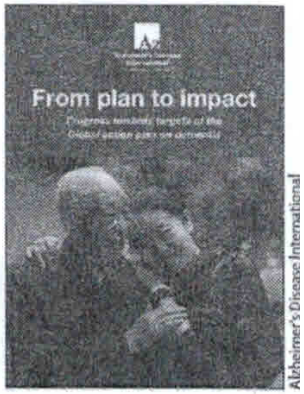
The Lancet Neurol. 17,651,2018

Response to the growing dementia burden must be faster

According to 2017 estimates from WHO, nearly 50 million people are living with dementia, and by 2030 the number is expected to reach 82 million. As this figure grows, so too will the need for support and care for people with dementia, which is projected to cost US$ 2 trillion globally by 2030. The need to prepare for and try to prevent some of this personal and financial burden has received increasing attention, most notably with adoption by the World Health Assembly last year of the WHO global action plan on dementia. One year on, a report from Alzheimer's Disease International (ADI), the global federation of Alzheimer's disease associations, shows that not enough progress has been made. Governments need to make dementia a higher priority and must take action quickly to prevent the burden of dementia from becoming overwhelming.

The overall goal of the WHO global action plan to be covered in future ADI reports, and currently too few data are available to assess progress towards the targets for support for carers, research and innovation, and diagnosis, treatment, care, and support. For the action area of information systems, the target is for 97 countries to collect a core set of dementia data by 2025, ideally through the WHO Global Dementia Observatory (GDO), a new platform for countries to share data on dementia indicators across all seven action areas. 21 countries have contributed to the pilot phase of the GDO, but even among these countries data are incomplete. If the ambitious WHO global action plan on dementia is to be successful, more member states need to start collecting and sharing their data through this platform.

Several initiatives are underway to accelerate progress and support member states that are willing to take action. On June 1, 2018, WHO published a practical guide to



Alzheimer's Disease International

For the **2017 WHO estimates of the burden of dementia** see http://www.who.int/mental_health/neurology/dementia/infographic_dementia/en/

For the **WHO global action plan on dementia** see http://www.who.int/mental_health/neurology/dementia/action_plan_2017_2025/en/

For the **ADI report** see https://