History of the Discovery of Alzheimer Disease

May 21st, 2019
# 303 Room F
3:30p-4:30p
Wisconsin Dells, WI

Piero Antuono MD
Prof. of Neurology and Biophysics
The Medical College of Wisconsin
Milwaukee WI.

History of the Discovery of Alzheimer Disease

……… to the present day

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Marco Tullio Cicerone 104-63 BC
Four Rules for Good Memory:
Arrange things to remember in a certain order
Relate to them with passion
Connect them to unusual images
Remember them with frequency

Tommaso D’Aquino in:
Librum de Memoria et Reminiscencia 1266
Causes of Dementia (Esquirol 1838)

**PHYSICAL CAUSES**
- Menstrual disorders
- Delivery
- Falls on the head
- Age
- Haemorrhoids
- Syphilis
- Excessive eating
- Wine abuse
- Masturbation

**MORAL CAUSES**
- Unhappy love
- Frights
- Political crises
- Unfulfilled ambitions
- Poverty
- Domestic grief

Publications in 1976: 53
Publications in 2018: 6,683
HISTOLOGY AND CLINICAL FINDINGS OF SOME PSYCHIATRIC DISEASES OF OLDER PEOPLE
Dr. Gastano Perusini
Munich, December 1908

On the suggestion of Dr. Alzheimer, I examined the following four cases. Case I. For the use of the case history and of the brain for microscopic research we thank Professor and Director Dr. Sioli of Frankfurt am Main.
Why was it called Alzheimer disease?

Importance of classification of disease according to age of onset

Competition with other research centers (O. Fisher)

Competition between the organic and functional Psychiatry (S. Freud)
Ugo Cerletti MD
1877-1963

Electroconvulsive therapy
1938
Alzheimer’s disease (1910-1967)

Described by Alzheimer
Early onset < 65 yrs. += Presenile Dementia
Rare condition

Senile dementia > 65
Inevitable w. age
Due to Arteriosclerosis


A Shocking discovery…

Blessed Tomlinson Toth 1968
Quantitative relationship between Alzheimer pathology and cognitive decline
Regardless of age

Vojtech Adalbert Kral
1903-1988

• 1903-1942: Prague (Otto Pötzl)
• 1942-1945: Theresienstadt
• 1945- 1948: Prague
• 1953: Director, Gerontology Division, Allen Memorial Institute, McGill University (First Gerontopsychiatric Department of the world?)
• 1972: London, Ontario

Benign senescent forgetfulness

• Kral (1958; 1962) was perhaps the first to notice that a complaint of memory loss is not necessarily a prodrome of dementia.
• Bamford and Caine (1988): The commonly used notion of "benign senescent forgetfulness" implies that such changes are part of "normal" aging and not associated with central nervous system pathology.

The Prevalence and Malignancy of Alzheimer disease

R Katzman MD
1925-2008

Archives of Neurology 1976, editorial

Senile dementia = Alzheimer disease
Alzheimer is an age related disorder
The world population is aging…

R Terry MD
1924-2017

Peter Davis UK 1976

Alzheimer has a cholinergic deficit

Luigi Amaducci Italy 1979

Peter Whitehouse USA 1983

Alzheimer has a cholinergic deficit

Pathology
Chemistry
Epidemiology

Alzheimer’s Disease: Senile Dementia and Related Disorders
Edited by
Robert Katzman, Robert D. Terry and John E. Ball

Aging of the Brain and Dementia
Edited by
L. Amaducci, A. R. Provenzale, P. Aronne

Raven
AD is a brain amyloidosis

- George Glenner
- Identified amyloid protein
- Vascular amyloid from Down syndrome
- Same protein present in Alzheimer’s disease
- AD is an amyloidosis
- 1984

AD is a brain amyloidosis

- Beyreuther K and Masters CL
- Sequenced amyloid protein
- Amyloid derived from APP
- “…It takes more than 10 yrs to develop a plaque…”
- 1985

Colin Masters

Konrad Beyreuther

Amyloid cascade hypothesis

- Mutation in APP, PDI, or PS2 genes
- Increased Aβ42 production and accumulation
- Aβ42 oligomerization and deposition as β plaques
- Subtle effect of Aβ on synapses
- Neuronal and astrogliotic activation (complement factors, cytokines, etc.)
- Progressive synaptic and neurologic injury
- Altered neocortical gene homeostasis; oxidative injury
- Altered kinase/phosphatase activities
- Widespread neurodegeneration and cell death with tangles/braids
- Dementia
Cascade Hypothesis

- 2002
- Dennis Selkoe, John Hardy
- Linking amyloid to other AD pathologies and defining the genetics

Imperial College of London
Harvard University

Stanley Prusiner UCSF
Nobel in 1997 for Physiology and Medicine

...discovered prions, a class of infectious self-reproducing pathogens primarily or solely composed of protein: Creuzfeld-Jacob disease

Tau in Alzheimer’s Disease Behaves Like Prion Protein

- CJD and related disorders are caused by non-viral proteinaceous infectious particles (prions)
- Proteins in Neurodegenerative diseases (NDD) have prion-like cell-to-cell transmission
Evolving Principles:
AD and NDD are proteinopathies

<table>
<thead>
<tr>
<th>Protein</th>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>Huntingtin</td>
<td>Huntington disease</td>
</tr>
<tr>
<td>ß-amyloid protein</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Alpha-Prion protein</td>
<td>Creutzfeld Jacob dis.</td>
</tr>
<tr>
<td>Synuclein</td>
<td>Parkinson’s disease, DLB</td>
</tr>
</tbody>
</table>

Proteins exist in different states of varying toxicity: (fibrils vs aggregates)

Proteins spread in a prion-like fashion

Prion spread along functional pathways (connectivity)

NDD are present in the brain before symptoms begin

NDD have genetic (as in the original case of Alzheimer) and sporadic forms