An approach to the prevention of Alzheimer’s dementia – can we get there from here?

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Alzheimer’s 1st reported case

First . . . jealous of her husband. Soon she “developed a rapid loss of memory. . . . disoriented in her home, . . . carried things from one place to another and hid them, . . . thought somebody was trying to kill her . . . When reading . . . skips from line to line or reads by spelling words individually . . . In writing, she repeats syllables, omits others, . . . In speaking, she uses gap-fills and paraphrased expressions (‘milk-pourer’ instead of cup); She no longer remembers the use of some objects. . . .”

“Auguste D.” 1903 - 4

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The rising pandemic of dementia

• Dementia is a syndrome that can have many causes

• Alzheimer’s disease (AD) is the most common neuro-degenerative disease of brain – causes 2/3 – 3/4 of all cases of dementia worldwide

• Today the world has >35 million cases of AD dementia. By 2050 this number will rise to 115 million cases . . . unless we learn to prevent AD dementia
The crushing costs of dementia

- In 2010, best estimates indicated worldwide costs > US $604 billion each year.
- Costs in Canada exceeded $5 billion / yr.
- By 2050, cumulative costs of Alzheimer care in U.S. estimated at $10,000,000,000,000 – $20,000,000,000,000,000 ($10 to 20 trillion) -- more than the current US government debt!
Crushing costs of dementia (2)

• By 2050, annual costs for 115 million cases worldwide X $20,000 / case = $2.3 trillion

• By 2050, 24% of Chinese population will be > age 65. Some 40 million with dementia.

• All this is foreordained unless we can learn to prevent AD dementia
Can we get there from here?
Yes!! If we understand that . . .

1. Alzheimer’s disease is a chronic disease, similar to heart disease and cancer.
2. The disease has a biology that extends well into the decades before symptoms are seen.
3. As we learn more about the biology of the disease, we will learn how to prevent or control it.
The “take home” messages (2)

4. Improved methods of detection and early intervention will undoubtedly motivate physicians and other health professionals to seek and treat early signs of disease.

5. We are “on the verge” of an explosion in knowledge about the biology of Alzheimer’s disease and the prevention of its symptoms.
The “take home” messages (3)

6. Prevention of Alzheimer’s dementia can be achieved without preventing the disease itself.

7. With research and resources similar to those dedicated to heart disease and cancer, we can achieve a similar measure of prevention – probably more!
Alzheimer’s disease

We know what it looks like . . .

Amyloid plaques

Neurofibrillary tangles
We don’t know the cause. But we do know that . . .

• Alzheimer’s is a chronic disease . . .

• It begins in sometime in middle life

• Its earliest symptoms are barely noticeable and may be viewed as “normal for age.”

• As symptoms become more severe they may be recognized as Mild Cognitive Impairment
Evolution in the Development of AD

Aggregation and misfolding of Aβ followed by plaques and tangles

Hypometabolism of AD vulnerable regions
Medial temporal lobe atrophy
Elevated CSF tau / Aβ ratio

Dendritic & cell death

“Latent” SCI MCI AD Dementia

Latent = No Cognitive Impairment
SCI = Subjective Cognitive Impairment
MCI = Mild Cognitive Impairment
AD = Alzheimer’s dementia

Birth 10 20 30 40 50 60 70 80 90 100

Years

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‘MCI’ – Is that where we should intervene?

- Significant compromise in cognitive ability leading to some difficulty in function, but . . .
- NO dementia (can maintain independent activity)
- Divided into types: amnestic (memory loss is predominant) vs. non-amnestic
- Amnestic type is thought to be the typical first blush (prodrome) of AD symptoms
‘MCI’ – What’s the story?

• Diagnosis is difficult to establish at first, but . . .

• Once it’s clear MCI is there, ~ 80% of those who have it will develop dementia within 10 years.

• Helpful for optimum management (medical advice, planning for future events)
However . . . .

Treatments for AD dementia have NOT been proven helpful for MCI, nor for delay of the later onset of dementia.

Has the train left the station?
More than half of people with MCI have a pathologic diagnosis of AD


The Neuropathology of Probable Alzheimer's Disease and Mild Cognitive Impairment

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Absolutely, we need to keep looking for better ways to care for and to treat people who already have symptoms, *but . . . . .*

Ultimately, we must find ways to attack the disease in its pre-symptomatic stages and prevent the emergence of symptoms.
Development of Alzheimer’s disease

- **Latent** = No Cognitive Impairment
- SCI = Subjective Cognitive Impairment
- MCI = Mild Cognitive Impairment
- AD = Alzheimer’s dementia

- Aggregation and misfolding of Aβ followed by plaques and tangles
- Hypometabolism of AD vulnerable regions
- Medial temporal lobe atrophy
- Elevated CSF tau / Aβ ratio
- Dendritic & cell death

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Can we do that?
Can we ‘get there from here’?
If so, how?
Two broad approaches:

1. Find and replicate factors that predispose some people to delay or avoid onset of dementia (‘lifestyle interventions’)

2. Pharmacological interventions keyed toward interruption of the disease process (‘disease modification’)
Several lifestyle intervention strategies appear to reduce risk of AD

- Regular exercise
- Reduce weight (Body Mass Index)
- Control blood pressure (in mid-life)
- Reduce insulin resistance and Type II (obesity-associated) diabetes
- Improved diet (“Mediterranean vs McDonald’s”)
What’s good for the heart is good for the brain!
But . . . rates of heart disease and stroke have come down enormously in the last few decades. Shouldn’t that mean that rates of AD dementia would also be dropping?
They are!!

• **Age-specific rates** are actually declining – for first time ever observed
• But the rapid aging of populations will more than offset any improvement in age-specific rates
• Effects of aging most clearly evident in the developing world
We can be glad for now.

• There really are things we can do to reduce our risk of AD dementia

• . . . but we won’t win the battle against AD this way. Ultimately, we’ll need to deal with the biology of the disease.

• How?
Biomarkers of AD may be useful for early diagnosis, before dementia is evident.

We may also be able to use biomarkers to measure the progress of AD in pre-symptomatic stage. . . .
‘Biomarkers’ of AD precede symptoms

Abnormal

Normal

Pre-symptomatic SCI MCI Dementia

FDG-PET
MRI hippocampal volume
CSF AB\textsubscript{42}
Cognitive performance
Function (ADL)
CSF Tau

Can we use biomarkers to measure the effects of prevention strategies?
‘Biomarkers’ of AD as measures of pre-symptomatic disease progress?

N.B. 'Biomarkers' of AD as measures of pre-symptomatic disease progress?

![Graph showing changes in biomarkers over time]

- CSF Aβ42
- CSF tau
- CDR-SOB
- Hippocampal volume
- Glucose metabolism

Estimated Yr from Expected Symptom Onset

Standardized Difference

-30 -20 -10 0 10

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Naproxen may diminish incidence of AD and reduce AD biomarkers in non-demented elderly

J C. Breitner et al. for ADAPT Research Group
Alzheimers and Dementia, 2011;7:402-11
Do you want to prevent Alzheimer’s disease?

Study conducted by the Centre for Studies on Prevention of Alzheimer’s Disease (StoP-AD) at the Douglas Mental Health University Institute.

Voulez-vous prévenir la maladie d’Alzheimer ?

Étude menée par le Centre de recherche sur la prévention de la maladie d’Alzheimer (StoP-Alzheimer) à l’Institut universitaire en santé mentale Douglas.
PREVENT-AD eligibility criteria

- 60 years old or more
  - 55-59 years old if 15 years within relative onset of AD

- Parent or 2 siblings with probable AD
  - mother and/or father; sister and/or brother

- Cognitively intact at entry
  - determined by MoCA and CDR

- Good general health

- Willing and able to participate in >5 yrs of annual assessments

www.prevent-alzheimer.ca
1-855-888-4485

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www.prevenir-alzheimer.ca
www.prevent-alzheimer.ca
1-855-888-4485
Ars longa, vita brevis
No time like the present . . .
Rome wasn’t built in a day!
Journey of 1000 miles begins with first steps

but . . . .

No sensible enterprise would commit than 0.5% of its expenditures to R & D
The “take home” messages

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Merci beaucoup!