LEARNING ABOUT ALZHEIMER’S THROUGH CLINICAL TRIALS
ABOUT ME

• General counsel and director of program development at Fox Hill Village, a CCRC

• Master’s in health policy

• Fellow at the Green House® Project

• Advisor, Hastings Center, a bioethics research center
  • Aging, Chronic Conditions and Care Near End of Life Sector

• My father and father in law both lived with dementia
WHITE OAK COTTAGES
WHITE OAK COTTAGES

• Assisted living dementia residence on Fox Hill campus

  - Green House adopter – attempting to radically change the way long term care is provided
  - Focused on quality of life and autonomy of residents
  - 2 cottages, 12 private bedrooms in each
FAMILIES SEEKING ANSWERS

- Is there a cure in sight?
- What can I do to prevent or delay the onset of this disease?
- How can I better understand scientific findings in the news?
WHAT CAUSES ALZHEIMER'S?

• Still trying to understand what triggers the disease process

• Rift within research world as to which protein accumulation should be the focus of research

• Study of lifestyle giving some information about possible protections

• Epidemiology critical to developing and confirming hypotheses
WHAT IS EPIDEMIOLOGY?

- Medical detectives trying to discover what causes disease and effective treatments
- Study of disease patterns among populations
  - Who gets sick?
  - Where?
  - When?
HOW IT WORKS

- Data driven science
- Requires statistical analysis
- Iterative in nature
- Different tools depending on focus of study
OBSERVATION OF POPULATIONS

- Observational studies of past exposures to identify source of disease
  - May not understand how exposure causes the disease, but can lead to preventative measures

- Develop a theory based on one case, or several cases

- Review data to determine if they support hypothesis
  - John Snow 1854 cholera outbreak
  - AIDS 1980s
  - Zika
PROSPECTIVE TRACKING

- Cohort study usually focused on understanding influences on specific diseases
  - Population without disease
  - Track going forward
  - Questionnaires
  - Physical exams and/or specimens
  - Can include study of specific exposures/activities
EXAMPLES OF COHORT STUDIES

Framingham Heart Study: risk factors for heart disease
www.framinghamheartstudy.org
• 1948: 5200 subjects
• 1971 5124 subjects
• 2002
• Omni studies 1994 and 2003

• Nurses Health Studies: oral contraceptive study
  www.channing.harvard.edu
• 1976: 238,000 subjects
• 1989: second generation 116,000 subjects
Clinical trials test the efficacy of potential treatments
Epidemiology is essential component

Phase I
- Safety, small group of healthy volunteers

Phase II
- Dosage
- Some measure of efficacy
- Larger group with disease in question

Phase III
- Clinical trials with controls
- Large groups, replications
CLINICAL TRIALS

- What is “gold standard”
  - Double blind
  - Placebo
  - Randomized

- Statistically significant outcomes
  - P value: probability that the effect observed could have happened by chance >.01 goal

- Peer Reviewed Publication

- Replication
APPLICATION TO ALZHEIMER’S

• Challenge of chronic disease investigation
  • Develops over many years
  • Likely to be result of multiple exposures

• Challenge of studying the brain

• Diagnosis not determinative without autopsy
What are biomarkers?
- Something that can be accurately and reliably measured to indicate presence of disease
- Not yet

“Hallmarks”?
- Amyloid and tau build up
- Shrinkage of hippocampus

2012: FDA approves Amyvid radioactive dye
VALIDATION ELUSIVE

- What FDA test suggested

- Led to realization that not everyone with Abeta had dementia;

- Some with dementia did not have Abeta

- Unresolved question of the role of Abeta and tau

- No scan test for Tau approved as of yet
CURRENT DRUG TRIALS

- Eli Lilly/NIH Solanezumab A4 Study
- Eli Lilly/NIH LEARN Study
- Biogen Aducanumab Phase 1 ➔ Phase III
Solanezumab: The A4Study: Can early treatment prevent or delay onset of cognitive decline?

- Joint study by NIH and Eli Lilly
- Screening 10,000 people, 60 different sites
- Ages 65 to 85
- All have Abeta build up, but no cognitive issues yet
- Results must show improvement in cognition and function
What are the non-amyloid drivers of cognitive decline?

- Offshoot of the A4 Study
  - 500 subjects rejected from A4 due to no amyloid

- Testing efficacy of new testing protocols for A4

- Tau sub-study with tau imaging agent TBD
  - 150 subjects (50 from LEARN; 100 from A4)

- Results in 2020
ADUCANUMAB

• Biogen trial

• Phase I results in July 166 subjects

• Showed dose dependent response at high doses

• High levels of side effects

• Phase III results expected 2018
WHAT CAN WE DO TO PREVENT OR DELAY ONSET?

- Diet
- Sleep
- Exercise
- Mental stimulation
- Social engagement
- Stress management
- Avoidance of some medications

- What do the epidemiologists have to say?
BEYOND CURE: WHAT WILL PROTECT?

FOODS

• Chocolate
• Red wine
• Ginko balboa
• Cocoanut oil
• Mediterranean diet
HOW TO LOOK AT FOOD

• Who conducted trial?
• How many subjects?
• How was it structured?
  • Randomized, double blind, placebo
• How long did trial last?
• Published in a peer reviewed journal?
• Replicated?
• Real food equivalents?
  Dosage calculation: how much food would you have to eat to get benefits described?
• **Prevagen**
  - Supplement not subject to FDA approval
  - Cease and desist due to no clinical trial
    - 56 subjects
    - Self-reported results
  - Class action suit
MENTAL STIMULATION

- Lumosity
  - Settlement with FTC for deceptive advertising
  - No credible trial showing improved general cognition
Multiple studies suggesting exercise improves cognition

Both in humans and animals

Measured by either size of hippocampus or brain activity during mental exercise
• APOE4 positive subjects
  • Those who exercised regularly showed greater brain activity when performing mental exercise.
  • Dose dependent
  • 68 people aged 65 to 85
  • Exercise self reported
  • Brain activity measured by MRI
  • P values < 0.033 and 0.014

• Walking study of 120 cognitively intact people
  • Aerobic exercise 4x/week vs. stretching exercises
  • Measured size of hippocampus by MRI
  • 2% increase in size in aerobic group, 1.4% decreased volume in stretching group
  • P values <0.001
POTENTIALLY DANGEROUS DRUGS

• Several well designed studies show an association between long term use and an increased risk of dementia

• Not known why the drugs are linked with risk; could be circumstantial

• Provides tools for further study
POTENTIALLY DANGEROUS DRUGS

• Sedating and anti-nausea meds (Benadryl, Sominex, Dramamine)
• Followed 3500 people in Seattle health plan for 7 years
  • Had access to pharmacy records
  • Use of anti-cholinergics associated with development of dementia
  • P value < 0.001
  • Published in JAMA, March 2015

• Acid reflux medications (Prilosec, Nexium, Prevacid)
  • German study of 73,000 subjects over 7 years
  • 44% increase in development of dementia for those taking drugs for more than 18 months
Are fewer people developing dementia?

- Framingham Heart Study
  - 44% decline in rate since 1970s
  - Limited to those with a high school education
    - Better diet?
    - Meds for stroke and heart?

- Stay tuned!
INFORMATION ON CLINICAL TRIALS

• clinicaltrials.gov

• nia.nih.gov/alzheimers/clinical-trials

• http://www.alz.org/research/clinical_trials/clinical_trials_alzheimers.asp
SUMMING IT UP

• No drugs to cure, slow or delay in near future
• Pro-active steps may provide protection
  • Healthy diet
  • Exercise
  • Sleep
  • Cognitive reserve?
• Cautious use of other drugs
• What is good for the heart is good for the brain; data is suggesting that prevalence is dropping