Dementia: Scope, Neuroscience, and Relevance for the Judiciary.

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Disclosures

No actual or potential conflicts of interest to disclose.
Perspectives represented

- **Clinical**: psychiatry (*geriatric psychiatry*): dementia at the level of the individual patient.
- **Research**: epidemiology (*neuroepidemiology*): dementia at the level of the community or population.
- **Influences**: neurologists, neuropsychologists, demographers, biostatisticians, imaging experts; earlier speakers and audience members at this seminar!
Ruvo Center for Brain Health, (Las Vegas) designed by Frank Gehry
% of population aged 65+ years

2008

2040

Less than 3.0%  3.0% to 4.9%  5.0% to 10.9%  11.0% or more

Epidemiologic (Demographic) Transition

Survival Curves for US women, 1901 and 2003

Sources: U.S. Census Bureau, 1936; and Arias, 2006.
Population Prevalence of Dementia by Age

5%-10% of individuals aged 65+; doubling every 5 years of age
## Population Burden of Disease

<table>
<thead>
<tr>
<th>Rank</th>
<th>Condition</th>
<th>Years lost to Mortality</th>
<th>Years lost to Disability</th>
<th>Disability-adjusted Life Years</th>
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<td>Heart disease *</td>
<td>20.5</td>
<td>Depression</td>
<td>8.0</td>
</tr>
<tr>
<td>2</td>
<td>Stroke</td>
<td>8.3</td>
<td>DEMENTIA</td>
<td>5.6</td>
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<td>3</td>
<td>Lung Cancer</td>
<td>6.3</td>
<td>Asthma</td>
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<td>Suicide</td>
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<td>Colorectal cancer</td>
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<td>6</td>
<td>COPD **</td>
<td>4.0</td>
<td>Diabetes mellitus</td>
<td>3.8</td>
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<td>Traffic accidents</td>
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<td>Alcohol dep/abuse</td>
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<tr>
<td>8</td>
<td>Breast Cancer</td>
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<td>COPD **</td>
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<tr>
<td>9</td>
<td>Diabetes mellitus</td>
<td>2.1</td>
<td>Stroke</td>
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<tr>
<td>10</td>
<td>DEMENTIA</td>
<td>1.8</td>
<td>Heart disease *</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Ischemic heart disease; ** Chronic obstructive pulmonary disease

**Australian Burden of Disease Study**
Costs of Alzheimer’s Disease *

- Recently estimated total costs of AD in the US: $148 billion annually, plus $89 billion in unpaid caregiving. *Alzheimer’s Association 2008.*
- The top 10% of Medicare beneficiaries with AD account for nearly half of total health expenditures and a third of drug expenditures. *Lin et al, 2009.*
- Different studies have reported a wide range of annual direct costs.
- Comparisons should be made cautiously because of marked variation in assumptions, methods, and health care financing systems.

*No U.S. Figures for costs of all dementias combined*
Dementia ...

• ...is common.
• ...will become even more common.
• ...is disabling.
• ...is expensive

So: what exactly is it?
Dementia is a generic term

*as currently defined:*

• Cognitive impairment: loss of cognitive/intellectual functioning from a previously higher level;
• Involves at least two domains of cognition, including memory.
• Sufficient to interfere with everyday social and occupational functioning, e.g. problem solving, relationships, everyday activities
• **A syndrome, not a disease;** dementia is caused by one or more diseases;
• May or may not be progressive, depending on the underlying cause.
• In older adults, Alzheimer’s disease (**AD**) is the single most common cause.

Mild Cognitive Impairment (MCI)

• Relatively new term.
• Refers to a state of impaired cognition, worse than expected for age, but not bad enough to be called dementia (not sufficient to cause loss of independent functioning).
• Can be an early stage of disease and a precursor of dementia, but is not necessarily so.
Structure of the brain

• The brain is made up of billions of *neurons* (nerve cells).

• Neurons have 3 functions:
  – To *communicate* with one another;
  – To break down chemicals and generate energy/build new proteins (*metabolism*);
  – To *maintain and repair* themselves.
The brain and normal aging

• 3 major functions of neurons:
  – Communication
  – Metabolism
  – Repair

• All these processes slow down with age.

• The normally aging brain has the capacity adapt/compensate.

• Normal older adults can continue to carry out most brain functions if given enough time.
The brain in dementia

• Depending on the brain disease causing the dementia, the basic functions (communication, metabolism, repair) of the neurones are lost in various parts of the brain.

• Depending on the brain region that is primarily affected, the individual experiences different symptoms and deficits.
Spectrum of brain dysfunction

Charting the Course of Healthy Aging, MCI, and AD

- AD brain changes start decades before symptoms show
- Amnestic MCI: memory problems; other cognitive functions OK; brain compensates for changes
- Cognitive decline accelerates after AD diagnosis

Life Course:
- Birth
- 40
- 60
- 80
- Death

- Healthy Aging
- Amnestic MCI
- Clinically Diagnosed AD

www.nia.nih.gov
Causes of dementia and cognitive impairment

- **Neurodegenerative diseases** (where brain cells themselves deteriorate); e.g. AD, Lewy Body Disease, frontotemporal lobar degeneration (FTLD), Parkinson’s, Huntingdon’s.

- **Cerebrovascular disease**: (where blood vessel disease compromises blood supply to the brain; strokes, white matter disease).

- **Infectious diseases** (e.g. HIV/AIDS, Creutzfeldt-Jakob, BSE or “mad cow”)

- **Trauma** (head injury: veterans; football players; motorcyclists)

- **Metabolic conditions**: thyroid disease, vitamin B-12 deficiency, etc.

- **Substance-induced**: e.g. alcohol, toxins

- **Normal-pressure hydrocephalus** resulting from some of above.

- **Congenital disorders**, such as “storage diseases” due to specific enzyme abnormalities, usually occurring in children and younger adults.
Causes of Dementia: relative frequency

• *Depends in part on diagnostic system being used and in part on the setting.*

• Alzheimer’s Disease is the most common single cause, in the elderly (70-90%).

• Vascular dementia (VaD) (due to cerebrovascular disease) is the next most common cause.

• The combination of AD and VaD is probably the most common; *BUT* vascular disease is almost ubiquitous in the very old.

• Other causes appear to be rare, ~ 10% of cases.
Prototype: Alzheimer’s Disease (AD)

• First reported in 1906 by Professor Alois Alzheimer:

• A 51 year-old woman admitted to a mental hospital in Germany with marked changes in mood and behavior and significant intellectual deterioration.

• These clinical symptoms and signs (dementia), together with the subsequent autopsy findings ("amyloid plaques" and "neurofibrillary tangles") in her brain, comprised the classical picture of AD.
Alzheimer’s Disease

• Alois Alzheimer, 1907:
  • single case report;
  • rare disease of middle-aged;
  • (pre-senile dementia).
Clinic v. Community Diagnosis: Completing the Clinical Picture

• Alois Alzheimer, 1907:
  • Single case report;
  • Rare disease of middle-aged;
  ("pre-senile dementia")

• Martin Roth and colleagues, 1964:
  • Community survey;
  • Fairly common disease of elderly; about 5% of those aged 65 years and older.
  ("senile dementia")
Clinic v. Community Diagnosis: Completing the Clinical Picture

• Alois Alzheimer, 1907:
  
  Rare disease of middle-aged
  (“pre-senile dementia”)

• Martin Roth and colleagues, 1964:

  Fairly common disease of elderly
  (“senile dementia”)
AD pathology: “Amyloid Cascade”

- The “cause” is not known but the process is fairly well understood.
- A protein called *amyloid precursor protein* (APP) gets snipped in the wrong place, releasing a fragment called β (*beta*) *amyloid*. These fragments clump together and form larger clumps called *oligomers*, start reacting with the neurons and interfering with their functioning.
- Oligomers grow larger and become *fibrils*, which eventually form amyloid *plaques*.
- Ongoing debate as to whether the plaques themselves damage the neurons or whether plaques represent the brain’s efforts to keep the β-amyloid sequestered away from the neurons.
**AD pathology: Neurofibrillary Tangles**

- Healthy neurones contain structures called *microtubules* which allow transport of nutrients and other chemicals.
- A protein called *tau* helps stabilize these microtubules.
- In AD, the tau protein attracts too many phosphate molecules and becomes “*hyperphosphorylated*”; it disengages from the tubules and starts to form *tangles*;
- The microtubules disintegrate and the neuron can no longer communicate with other neurons.
AD pathology: Synaptic Loss and Cell Death

• When neurons can no longer communicate with each other, they die.
• The “synapses” between neurons, where the communication between neurons takes place, become fewer.
• As cells die in a given region, that region undergoes atrophy (shrinkage).
AD and the Brain

• The disease begins deep in the brain (entorhinal cortex)
• Spreads to the hippocampus, and then to other parts of the cortex.
• As the cells in the affected areas start to die, the areas shrink (atrophy) visibly.
• These cells are responsible for producing and using a chemical messenger (neurotransmitter) called acetylcholine which is essential for memory.
The brain in AD

Early stage

Middle stage

Late stage
Normal brain vs. Alzheimer’s disease brain
What can be seen on tests? (1)

• **Atrophy** (shrinkage); whole brain, certain regions (hippocampus and medial temporal lobe); can be seen at autopsy; can be seen on CT scan and MRI scan.

• **Amyloid plaques**, (previously called senile plaques) which are found in the tissue between the neurons (nerve cells). *A few plaques are present in normal aging.* Classically found at autopsy; can be seen on PET scan after injecting a radioactive tracer which binds to amyloid.

• **Neurofibrillary tangles** are largely made up of a protein called **tau**. Cannot at present be seen on scans.
What can be seen on tests? (2)

- **β-amyloid and tau can be measured in cerebrospinal fluid; requires lumbar puncture (spinal tap) to extract the fluid and perform the assay. The ratio of β-amyloid to tau is being researched as biomarker of AD.**

- **Lewy bodies** - structures containing a protein called α-synuclein, seen in about a quarter of cases of AD; they are typical of Parkinson’s disease (PD); they characterize a third condition called Lewy Body Dementia (LBD) or Dementia with Lewy Bodies (DLB) which has features of both AD and PD, also has hallucinations and other symptoms. Not required for diagnosis of AD and cannot be visualized on brain scans.
Genetics: quick overview.

- We have 23 pairs of chromosomes.
- We inherit one of each pair from each parent.
- Genes instruct the body to make specific proteins.
- Proteins have different functions; different forms of the same protein can perform those functions with greater or lesser effectiveness.
- Some proteins (therefore also the corresponding genes) cause disease.
- An autosomal *dominant* gene causes disease if the person inherits even one copy (i.e. if even one parent has disease).
- An autosomal *recessive* gene causes disease only if two copies are inherited.
Genetics of AD (1)

• 3 autosomal dominant “deterministic” genes for early-onset (before age 60, often before age 50) AD.
  – Amyloid Precursor Protein (APP) gene on Chromosome 21,
  – Presenilin 1 (PS1) gene on Chromosome 14,
  – Presenilin 2 (PS2) gene on Chromosome 1.

• All 3 seem to cause excessive production of amyloid.
• All 3 are rare, and account for less than 5% of all AD.
Another gene is fairly common, and is not deterministic; rather it is a “susceptibility” gene; increases probability of getting AD.

This is the Apolipoprotein E (APOE) gene on Chromosome 19; it is polymorphic and has 3 forms: APOE*2, APOE*3, and APOE*4.

APOE*3 is the most common. APOE*4 elevates the risk of AD; APOE*2 lowers the risk of AD, and is quite rare.
**APOE**

- The *APOE* gene tells the body to make ApoE protein, which has the corresponding 3 forms: ApoE2, ApoE3, ApoE4.
- The better-known function of ApoE is to *clear away cholesterol*; it *also clears away amyloid*.
- People with *APOE*4 are at elevated risk of heart disease.
- They are also at elevated risk of developing AD, *except*:
- People of African descent are more likely to have the *APOE*4 gene (than Caucasians and Asians) but *APOE*4 does not seem to significantly elevate AD risk in Africans and African-Americans.
- Being *homozygous* (having 2 copies of the gene) increases risk more than being *heterozygous* (having one copy).
Genetics and AD in a nutshell

- If one of the known mutations (APP, PS1, PS2) is present, the person is pretty likely to develop AD (not necessary but sufficient).

- If the risk gene $APOE^*4$ is present, the person is at elevated risk of getting dementia but may not get it (neither necessary nor sufficient).
Genes for other dementias

• Vascular dementia:
  – APOE*4 could play a role
  – CADASIL: cortical autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy: gene called NOTCH3

• Huntingdon’s disease: autosomal dominant gene on chromosome 4. *

• Frontotemporal dementia (some cases associated with genes on chromosomes 3 and
  
  ____________

* diagnostic
Symptoms and signs of AD

as currently defined:

• Decline in functioning in two or more cognitive domains including memory, (and other domains such as executive, language, and visuospatial function);

• The above are sufficient to interfere with everyday functioning.

• Frequently, behavioral disturbances:
  – Early in the disease course: personality change, withdrawal, anxiety, depression, apathy, irritability, poor judgment.
  – Later in the disease: delusions, agitation, aggressiveness, hallucinations.
  – Emotional lability

• Usually, loss of insight, judgment, sensitivity, empathy, social awareness.
Cognitive Functions Lost in Dementia

- **Attention/concentration.**
- **Speed** of processing.
- **Executive Functions** (planning, organizing, “multitasking,” problem-solving).
- **Memory** (initial learning, subsequent recall). Recent memory is lost before remote memory.
- **Language** (understanding as well as communicating; naming; wordfinding; fluency).
- **Visuospatial** function or praxis (using and manipulating non-verbal visual material, e.g. telling time from a clock; assembling items from parts; operating appliances; dressing, feeding).
Behavioral Functions Lost in Dementia

- Emotional control: ability to display emotions that are appropriate in nature and amount;
- Normal inhibition: ability to regulate behavior in accordance with societal and own previous standards of appropriateness.
- Spontaneity/Initiative: people can become apathetic and passive.
- Insight: people may not recognize their own deficits.
Behavioral Functions Lost

• Judgment:
  – financial decisions: bill-paying; handling money; investments; susceptibility to exploitation or scams;
  – inappropriate language or behavior towards others, out of character;
  – other poor decisions – at work, at home, in social situations.
Other Behavioral Symptoms

- Mood: anxiety, depression, irritability, anger
- Delusions*: false beliefs (sometimes resulting from real phenomena, e.g. misplaced objects are assumed to have been stolen).
- Hallucinations*: not very common; usually visual rather than auditory.
- Agitation, pacing, wandering.
- Aggressiveness.

* “psychosis”
Course and Outcome in AD

Over time, individuals become progressively:

• more severely cognitively impaired;
• more functionally disabled;
• more dependent on others for everyday needs; initially with, e.g. money management, medication management, using household appliances, operating motor vehicles;
• eventually unable to dress, feed, toilet, ambulate, speak, recognize familiar people and locations.
Definitive Test for AD

• None, according to current definition.
• The definitive diagnosis of AD is based on brain pathology; requires autopsy since we don’t typically do brain biopsy.
Diagnosis of AD

Diagnosis during life is based on the preponderance of the evidence.

Experienced clinicians recognize the typical history and symptoms/signs and course: (insidious onset and gradual progression of dementia)

Prominent and early loss of memory and executive functions (objective neuropsychological testing is valuable and can be used to track change over time).

Often depression, apathy, anxiety, other behavioral changes as well.
Supportive Evidence for AD Diagnosis

- Absent evidence of other causes of dementia (although they can co-exist with AD)
- Brain scan (MRI better than CT) should show diffuse overall atrophy, enlarged ventricles, and often atrophy specifically in the entorhinal cortex and hippocampus.
- SPECT scan may show typical blood flow pattern; FDG-PET scan may show reduced glucose metabolism.
- The deterministic genes (APP, PS1, PS2) in very rare familial cases. (*Not* APOE)

Under investigation:
- PET scan for amyloid in the brain (will not show oligomers, only fibrils and plaques)
- Spinal fluid may show abnormal ratio of β-amyloid to tau.
Diagnosis of Vascular Dementia (VaD)

- Caused by big or small strokes (infarcts) or greatly compromised blood circulation in the brain.
- History of heart disease, high blood pressure (hypertension), strokes.
- Dementia may be of sudden onset, and may progress in a stepwise fashion.
- Impaired cognitive domains depend on which region of brain was affected.
- Memory may not be one of the impaired functions.
- MRI scan will show infarcts (“lacunes”) and white matter hyperintensities.
MRI in Vascular Dementia
Co-morbidity

• AD can co-exist with VaD; in fact it usually does.
• So, evidence of strokes etc does not “rule out” AD.
• Having both brain diseases together can make the dementia more severe, or manifest earlier, or go downhill more rapidly.
• If AD co-exists with a treatable condition like depression or thyroid disease, treatment of the latter usually improves the dementia but does not arrest or reverse the AD.
Currently available drugs approved for the treatment of AD provide modest benefit in slowing the rate of decline but are not disease-modifying:

• *cholinesterase inhibitors* (raise level of acetylcholine in the brain)

• *glutamate modulator* (helps minimize excitotoxicity)

There are also effective *psychotropic* drugs for symptom relief of many behavioral manifestations, although with some risk.
Non-drug treatment of AD

• Psychotherapy, cognitive training, and compensatory strategies for the patient earlier in the course of the disease.
• Behavioral strategies later in the course.
• Counseling, education, and resource coordination for caregivers throughout the disease course.

THESE ARE EXTRAORDINARILY IMPORTANT but do not cure, arrest, reverse the disease process.
Excellent Resources

• Alzheimer’s Association
  www.alz.org

• National Institute on Aging
  Alzheimer's Disease Education and Referral (ADEAR) Center
  http://www.nia.nih.gov/ alzheimers
Treatment of Other Dementias

- The degenerative diseases cannot be cured, arrested, reversed, or controlled at present.
- Cerebrovascular disease (leading to VaD) can be controlled up to a point, by avoiding or limiting stroke risk factors.
- Dementias caused partly or entirely by treatable conditions (e.g., thyroid disease, toxins) can be arrested or even reversed, but these are rare.
Treatment of Comorbid Condition

If AD co-exists with a treatable condition like depression or thyroid disease, treatment of the latter usually improves the dementia but does not arrest or reverse the AD.
Consequences for Caregivers

• Families acquire increasing responsibility;
• Suffer stress,
• Sometimes conflict with patient and/or other relatives;
• Typically suffer financial burdens:
  – Patient will have to stop working and lose income.
  – Caregiver may have to stop working to provide care;
  – May have to pay for adult day care or in-home aides;
  – May have to pay for long-term care facilities;
  – May have out-of-pocket costs for health care and medications.
Legal *Implications of Dementia

- Patient can be the victim of others: abuse, neglect, fraud.
- Patient can be accused of negligence or incompetence.
- Patient can be accused of harming others or property.

*I am not using the terms in any approved legal sense.*
Some Legal Implications of Dementia

• Informed consent for medical treatment and research.
• Commitment for involuntary treatment.
• End-of-life care: advance directives, initiate or terminate tube-feeding.
• Voting.
• Competency to carry out occupational responsibilities.
• Competency to act in own self-interest (financial transactions, trusts and wills, vulnerability to exploitation, medical decisions, hospitalization, admission to long-term care facility); need for durable power of attorney or guardianship.
• Individual with dementia may falsely accuse others.
More Legal Implications of Dementia

- Permanence of incapacity (*vis a’ vis* duration of disorder, likely response to treatment).
- Diminished responsibility for crimes, felonies, misdemeanors. (Do mental health laws e.g., insanity defense apply to dementia?)
- Competency to stand trial/ testify on own behalf/instruct counsel.
- Competency to serve as witness or plaintiff or juror.
- Personal and public safety issues (fitness to operate motor vehicles? access to firearms?)
- Liability for dementia caused by e.g. trauma or occupational exposure.
What are the clinical diagnostic questions?

- Does the person have dementia?
- What is the underlying cause of the dementia?
- Are there any treatable causes present?
What are the legal questions?

• Is there a dementia?
• Is the illegal behavior/ vulnerability attributable to the dementia?
• Should evidence of the dementia and its causes be admitted?
• Can the dementia be used as a defense (diminished responsibility, etc)?
• Can the dementia be used to mitigate the penalty?

(really does not matter what disease(s) underly the dementia)
Does technology help?

• Whether the dementia is due to Alzheimer’s or something else does not really address the legal issues.

• Technology (imaging, biomarkers, etc cannot distinguish between normal and dementia) only helps to narrow down the cause of the dementia e.g. AD.

• A person can be biomarker-positive but be clinically normal. (Biomarker may reflect underlying disease and predict future dementia).
How useful are the neuropsychological tests?

- Distinction between normal aging and very mild dementia can sometimes be difficult, depends on the availability of appropriate norms.
- A person with dementia cannot successfully fake normalcy during expert assessment.
- However, a person who is very bright/educated/high functioning can suffer some losses and still ace a test intended for “normal” people (*this is not faking good*).
- A normal person of different educational/cultural background may perform badly because of unfamiliarity with test format; *this is not faking bad.*
Malingering

- A normal person can fake dementia up to a point, but expert evaluation including neuropsychological assessment can usually help sort this out.
- The usual technique in malingering detection is to capitalize on the layman's misunderstanding of brain function.
Tests to distinguish dementia from malingering (1)

- Recognition (forced choice) formats look like memory tests but they are not.
  - *“which one of this pair of pictures have you seen before?”*
- Demented people do well on these tests (i.e., get almost all items correct - as do most 7 year olds) while fakers score way below this level and sometimes below chance.
Distinguishing dementia from malingering (2)

- The other major approach is to examine the relationship between easy and hard versions of tests.
- Malingers often do relatively poorly on the easy version of a test in relation to the hard version.
- As this ratio gets closer to 1, could suspect effort/motivation.
Detecting malingering

There are numerous variations on this format. Generally cut-scores are set to hold specificity (correct identification of non-fakers as such) at about 90-95% percent.

Since it is such a rare experience to trip any one of these type tests, if we string together 3 or more such performances in a typical battery, the odds of it being due to other than conscious malingering approach zero.
Prevention of dementia

• No definitive evidence based on double-blind randomized controlled trials.

• Observational data suggest that onset of AD symptoms may be delayed by:
  – Greater education, cognitive and social engagement, building “brain reserve” or “cognitive reserve;”
  – Physical exercise
  – Heart-healthy diet and lifestyle
  – Early and effective treatment of other conditions such as depression, heart disease, thyroid disease;
  – Light to moderate alcohol use

• No basis for “blaming the victim.”
THANK YOU

- AAAS
- Dana Foundation
- Federal Judicial Center
- National Center for State Courts
- ABA Judicial Division
- Washington University in St. Louis
- National Institute on Aging, NIH (US DHHS)
- University of Pittsburgh