The Railway workers wife and the Cannibal. Tales of Protein folding and Neurodegeneration.
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Proteins

Protein constitutes 17% of the human body.

Proteins carry out essential functional tasks, e.g. enzymes.

Proteins are 3-Dimensional creatures.

The primary sequence of the protein is encoded by the DNA (genes).
Proteins are 3-D Creatures.

https://youtu.be/qs3xONv548I
Protein Folding.

Primary sequence is the main factor controlling protein folding…..
But the internal environment of the cell, temperature, salt concentration (hydrophobicity).

Ribbons (arrows) and Corkscrews
Proteins Need to be Folded.

Disease

Clearance
Enough About Proteins. Let's Talk About The Brain.
# The Incidence of Some Common Neurological Disorders.

<table>
<thead>
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<tbody>
<tr>
<td>Alzheimer's</td>
<td>&gt;65</td>
<td>1,275</td>
<td>2,459,000</td>
<td>0.5</td>
<td>&gt;80</td>
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<tr>
<td>Stroke</td>
<td>&gt;65</td>
<td>1,093</td>
<td></td>
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<tr>
<td></td>
<td>All</td>
<td>183</td>
<td>2,956,000</td>
<td>1.1</td>
<td>&gt;80</td>
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<td>Parkinson</td>
<td>&gt;65</td>
<td>160</td>
<td>349,000</td>
<td>1.8</td>
<td>&gt;70</td>
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<tr>
<td>TBI</td>
<td>All</td>
<td>101</td>
<td></td>
<td>2.1</td>
<td>20, &gt;80</td>
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<tr>
<td>Epilepsy</td>
<td>All</td>
<td>48</td>
<td>2,098,000</td>
<td>1</td>
<td>10, &gt;80</td>
</tr>
<tr>
<td>SCI</td>
<td>All</td>
<td>4.5</td>
<td></td>
<td>4.2</td>
<td>20</td>
</tr>
<tr>
<td>MS</td>
<td>All</td>
<td>4.2</td>
<td>266,000</td>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>ALS</td>
<td>All</td>
<td>1.6</td>
<td>12,000</td>
<td>1.3</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

Does not include psychiatric disorders, migraine, autism peripheral neuropathies, pain conditions and early development problems.
The Railway Workers Wife and the Doctor.

Auguste Deter (1850-1906).
First diagnosed case of Alzheimer's disease.

Ich hab mich verloren
(I have lost myself).

Dr. Alois Alzheimer (1864-1915).
Alzheimers Disease.

Progressive disorder with 4 main recognized stages:

1) **Pre-dementia (mild cognitive impairment):** up to 8 years prior to criteria for an AD diagnosis. Often mistaken for stress/aging and associated with memory loss (ability to acquire new information and loss of recent facts).

2) **Early:** Increasing impairment of learning and memory becomes symptomatic. Problems with language, decision making, movement and perception. Newer memories more affected than older.

3) **Moderate:** Progressive deterioration such that normal living becomes very difficult. Motor skills impeded so that falling becomes a problem. Inability to recall vocabulary. Memory problems increase with old memories lost as well.

4) **Advanced:** Language down to a few phrases or complete loss of speech. Often immobile, simple motor functions difficult. Aggressive. Apathetic/exhausted. Unable to feed themselves. Death will occur through a secondary mechanism.
Neural Death in Alzheimer's Disease.
Plaques and Tangles are Hallmarks of Alzheimer's.

Amyloid Plaques Are Composed of A Small Misfolded Peptide.

The Aβ peptide is derived from a much larger protein that crosses the cell membrane.
The Amyloid Peptide.

Soluble aggregates.

Insoluble fibrils.
The Molecular Progression of AD.

- **Familial AD**
  - Misense mutations APP/Presen1 or 2 genes
  - Lifelong increase in Aβ production

- **Sporadic AD**
  - Non-dominant forms of AD
  - Failure of Aβ clearance mechanisms

**Increased Aβ levels in brain**

**Inflammatory response**

**Progressive neuritic injury**

**Oxidative injury**

**Hyperphosphorylated tau leading to PHF formation**

**Neuronal/neuritic dysfunction/death with neurotransmitter deficits**

**DEMENTIA**
1) Alzheimer's disease is a disease of aging. The risk doubles every 5 years after 65.

2) 20% of US population will be over 65 by 2030 (except me, I’ll be turning 40).

3) Over 85s are the fastest growing segment of US population.

4) 26.6 million individuals in 2006 and 1 in 80 globally by 2050.
Ahhhhh!!!!! So what can I do?
What Can You do?

There is little long-term evidence at the moment that any particular diet or life-style can prevent or slow Alzheimer's disease. However, observational studies have identified factors associated with increased rates. Therefore:

1) Exercise.

2) Eat Healthy.

3) Control cholesterol, type 2 diabetes, weight, blood pressure, smoking.

4) Get treatment for depression.

5) Sleep.

6) Be social and engage in stuff that makes you think.

www.nia.nih.gov/sites/default/files/preventing_alzheimers_disease_0.pdf
So What Happened to the Cannibal?

Paul Gadjusek (1923-2008)

In the 1950’s and 1960s Gadjusek worked among the South Fore tribe of Papua New Guinea, where the Disease of Kuru was rampant. Gadjusek connected the disease with the practice of funerary cannibalism.
Kuru. The laughing disease?
Kuru

A wasting disease that affects people who practice funerary cannibalism.

Onset 20s-30s.

Muscle twitches and contractions.

More common among women than men.

Weakness, wasting, confusion.

Death within 6-12 months.
So That’s the Cannibals What About the Rest of us?
Transmissible Spongiform Encephalopathies.

**Scrapie:** Disease among sheep and goats (chronic wasting disease in deer).

**CJD:** (Creuzfeld-Jacob Disease). Sporadic, familial and variant (1:2000, frequency in UK).

**Kuru:** Extinct?

In 1982-84 Stanley Prusiner isolated a protein particle which was the infectious agent. He termed the phrase Prion. Received the Nobel Prize in Medicine (1997).
Prions: What Happens When You Don’t Fold Properly

Prions are more resistant to disinfectants/sterilants than most microorganisms and viruses.

**Normal**
Soluble and degradable
(Corkscrews good)

**Prion**
Insoluble and non-degradable
(arrows bad)
(The Amyloid fold)
Prions: Zombies of the Protein World.

Sporadic CJD (sCJD)
Familial CJD (fCJD)
Variant CJD (vCJD)
Prions Also Assemble into Fibrils.
**Protein Aggregates and Neurodegeneration.**

Table 1 Neurodegenerative diseases: proteins and pathology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Regions most affected</th>
<th>Characteristic pathology</th>
<th>Disease proteins deposited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington's disease</td>
<td>Huntingtin (dominant)</td>
<td>Striatum, other basal ganglia, cortex, other regions</td>
<td>Intranuclear inclusions and cytoplasmic aggregates</td>
<td>Huntingtin with polyglutamine expansion</td>
</tr>
<tr>
<td>Other polyglutamine diseases (DRPLA, SCA1–3, etc., SBMA)</td>
<td>Atrophin-1, ataxin-1–3, etc.; androgen receptor (AR) (dominant)</td>
<td>Basal ganglia, brain stem, cerebellum, and spinal cord</td>
<td>Intranuclear inclusions</td>
<td>Atrophin-1, ataxins or AR</td>
</tr>
<tr>
<td>Alzheimer's disease (AD)</td>
<td>Sporadic (ApoE risk factor)</td>
<td>Cortex, hippocampus, basal forebrain, brain stem</td>
<td>Neuritic plaques and neurofibrillary tangles</td>
<td>Aβ peptide (from APP) and hyperphosphorylated tau</td>
</tr>
<tr>
<td></td>
<td>Amyloid precursor protein (APP) (dominant)</td>
<td>Same as sporadic</td>
<td>Same as sporadic</td>
<td>Same as sporadic</td>
</tr>
<tr>
<td></td>
<td>Presenilin 1, 2 (dominant)</td>
<td>Same as sporadic</td>
<td>Same as sporadic</td>
<td>Same as sporadic</td>
</tr>
<tr>
<td>Fronto-temporal dementia with Parkinsonism</td>
<td>Tau mutations (dominant)</td>
<td>Frontal and temporal cortex, hippocampus</td>
<td>Pick bodies</td>
<td>Hyperphosphorylated tau protein</td>
</tr>
<tr>
<td>Parkinson's disease (PD)</td>
<td>Sporadic</td>
<td>Substantia nigra, cortex, locus ceruleus, raphe, etc.</td>
<td>Lewy bodies and Lewy neurites</td>
<td>α-Synuclein</td>
</tr>
<tr>
<td></td>
<td>α-Synuclein (dominant)</td>
<td>Similar to sporadic, but more widespread</td>
<td>Similar to sporadic</td>
<td>α-Synuclein</td>
</tr>
<tr>
<td></td>
<td>Parkin (also DJ-1, PINK1) recessive (some dominant)</td>
<td>Substantia nigra (or much less frequent)</td>
<td>Lewy bodies absent</td>
<td>α-Synuclein (when present)</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>Sporadic</td>
<td>Spinal motor neurons and motor cortex</td>
<td>Bonina bodies and axonal spheroids</td>
<td>Unknown (neurofilaments)</td>
</tr>
<tr>
<td></td>
<td>Superoxide dismutase-1 (dominant)</td>
<td>Same as sporadic</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Prion diseases (kuru, CJD, GSS disease, fatal familial insomnia, new variant CJD)</td>
<td>Sporadic, genetic and infectious</td>
<td>Cortex, thalamus, brain stem, cerebellum, other areas</td>
<td>Spongiform degeneration, amyloid, other aggregates</td>
<td>Prion protein</td>
</tr>
</tbody>
</table>

ApoE, apolipoprotein E; APP, amyloid precursor protein; CJD, Creutzfeldt–Jakob disease; DRPLA, dentato-rubral and pallido-Luysian atrophy; GSS, Gerstmann–Straussler–Scheinker; SBMA, spinal and bulbar muscular atrophy; SCA, spino-cerebellar ataxia.

So what have I heard?

1) Neurons are long-lived and are meant to last the lifetime of the brain. A balance exists between the synthesis and degradation of proteins. When this balance is lost proteins can accumulate resulting in aggregates or fibrils that can contribute to disease. Accumulation of misfolded proteins in a similar fashion can also result in disease.

2) Leading a healthy lifestyle is good. Factors that lead to oxidative damage of a protein can exacerbate protein accumulation and promote disease.

3) Leading a Zombie lifestyle is bad.
That's right, Four Eyes! You're nothing without me! While I'm an essential part of any protein, even yours, you're still a so-so professor with no chance of tenure! HAHAHA!

A mean o' acid