The Prion Story: History, Film & Treatment (?)

William A Jet Broughton, MD
Professor of Medicine USA-COM
Division of Pulmonary, CCM, and Sleep Medicine

Ice-9

In the 1930s GE invited famed sci-fi author H.G. Wells to visit their laboratories. The soon-to-be Nobel prize winner Irving Langmuir was assigned the task of entertaining him.

Langmuir conceived of a story about a fictional 9-molecule polymer of water he called "Ice-9"

He suggested a “seed-crystal” that caused whatever body of water it contacted to crystallize in a very stable ICE-9 polymer form

“ICE-9” would only melt at 114.4°F

Langmuir hoped that Wells would find the concept interesting enough to include it in a later novel.

Wells did not – ICE-9 was temporarily forgotten.
Ice -9

• Kurt Vonnegut went to work for GE in the public relations department after his military service (and POW time) in WWII
• It was there he discovered the reports of the Langmuir / Wells meeting in the ’30s and the story of Ice-9
• He was a young novelist at the time and decided that since no one had used the concept…he would “borrow it”.
• In 1963 he wrote one of the many novels that made him famous…

Cat’s Cradle

• Felix Hoenikker – the fictional father of the atomic bomb – a “pure researcher”
• Someone once mentioned the task of solving the “mud” problem for the US infantry
• Thus: the Ice-9 crystal – one tiny chunk into the offending mud that was obstructing military advance and they could simply walk/drive over it
• One problem: If Ice-9 got into a large body of water the world’s water might freeze over permanently
• Unfortunately, Hoenikker dies suddenly in the novel leaving 3 small Ice-9 crystals in the hands of his “less-than-sane” kids
• The outcome is predictable

What does Ice-9 have to do with prions?

• Before these ideas, the concept that “rogue” molecular conformations could arise and have serious real-world repercussions was only the subject of fantasy (although such things did happen in crystal formation)
• In truth, what was then fodder for science fiction novels was already on the planet and is now the subject of multi-million dollar medical research
• And now a tale of animals and men…

Death in Venice

In the mid-18th century, in a home in Venice just off Campo Santi Apostoli, a late-middle-aged physician fell ill.

His associates had no idea what was wrong with him.

Over 15 months he deteriorated and eventually died despite what treatment they could offer
Death in Venice

- The physicians of the day were at a loss
- They blamed encephalitis, occult alcoholism, an unknown infectious illness…essentially all the things we blame today when we don’t understand (we blame the patient!)
- As the years passed, other family members began to die in middle-age with similar symptoms
- The physicians of the day still had no answers and routinely blamed alcoholism (even when there was no history)
- The family saw the illness as a curse, they could easily recognize the onset of symptoms, knew the course of the illness, and they spoke of it to no one…

The Symptoms: Death in Venice

<table>
<thead>
<tr>
<th>Early symptoms</th>
<th>Late symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diaphoresis</td>
<td>- Insomnia – sleep only light stupor</td>
</tr>
<tr>
<td>- Miosis</td>
<td>- Loss of balance**</td>
</tr>
<tr>
<td>- Odd head posture*</td>
<td>- Alternating lucidity and hallucinations</td>
</tr>
<tr>
<td>- Constipation</td>
<td>- Finally: bed-bound, sleepless and fully aware of their own impending death</td>
</tr>
<tr>
<td>- Impotence</td>
<td></td>
</tr>
<tr>
<td>- Wide fluctuations of pulse and B/P</td>
<td></td>
</tr>
<tr>
<td>- Exhaustion</td>
<td></td>
</tr>
</tbody>
</table>

Sheep and Scrapie

In England by the 1700's it was becoming apparent that the land available for farming would not support the growing population.

A sheep farmer – Robert Bakewell – had the idea that breeding in-and-in of the most meaty sheep - could produce sheep with more meat per hoof

Without regard for the possible ill-effects of in-breeding he did just that – producing the Dibley Leicester sheep pictured above.

Sheep and Scrapie

- Bakewell’s Idea worked well
- Sheep with tiny heads and spindly legs were readily bred - called “a water tank on 4 legs”
- In 1710: sheep were 28# / lambs 18#
- by 1795: Sheep were 80# / lambs 50#
- Breeding in-and-in was a commercial success – even if a lamb’s great-great grandfather was also his father
- This process became routine herd management / animal husbandry

Sheep and Scrapie

- Enter Sir Joseph Banks – wool entrepreneur / botanist / scientist
- Britain was spending 1M pounds a year on Spanish Merino wool – the finest available in the world
- The Spanish owned the Merino herds and would not sell sheep to the British
- When above-board dealings failed – sheep smuggling ensued (1787)
- The British then began their own cross-breeding for wool / in-and-in style

Sheep and Scrapie

Merino wool is plentiful, fine and even “greasy”. The folds of these sheep supply large amounts of wool per animal.

But there was a secret about the Merino sheep the British did not know.
Sheep and Scrapie

- It was Thomas Comber that first reported a problem with sheep in Huntingdonshire.
- He described “a terrible itch” occurring in some sheep that would cause them to rub the wool off their rump, assume an odd tilt to the head*, develop a “distant” & “goggle” look to the eyes, show hypersexual behavior, and a tiredness.
- Eventually the animals would stand with their heads resting on the ground as if asleep – they usually died at night.
- The condition/disease appeared to be spreading.
- The head of the Royal Society of London would not speak publicly about the problem for fear of a negative economic impact on the sheep industry.
- The head of the Royal Society was Sir Joseph Banks.

Scrapie

The Spaniards knew all about scrapie and experienced shepherds were able to recognize it early and cull the affected sheep from the herd. British suspected a conspiracy to send them diseased sheep – never proven.

The British sheep herds were decimated – Banks eventually sent healthy sheep herds to Australia and stopped the in-and-in breeding in the early 1800’s. By 1913 scrapie was considered “an obscure disease of sheep.”

Creutzfeldt-Jakob Disease

- 1910 H.G. Creutzfeldt described a 23 y/o female (Berta) with dementia, red skin, loss of ambulation*, shaking, and hysterical behavior that progressed to fever-coma-death.
- Brain pathology at autopsy showed dead neurons everywhere.
- He published his findings in 1920.
- Alfons Maria Jakob described a series of middle-aged men and women with similar symptoms to those of Creutzfeldt.
- He thought the diseases and pathology were similar.
- Later reviews have suggested that some of these patients did not have CJD.
- Initially thought a very rare disease with only 986 UK victims identified by 1990-2007.
- The incidence in US is thought to be 1 case per million persons (?)
Creutzfeldt-Jakob Disease

Dementia with myoclonic jerks

Early symptoms for both sporadic and iatrogenic CJD can include:
- Mood changes
- Depression
- Anxiety
- Memory changes
- Apraxia
- Akinetic mutism
- Drowsiness or lack of coordination

There is no cure – death is inevitable

Pulvinar and ribbon signs in sporadic CJD

sCJD - characteristic EEG periodic bi-/tri-phasic sharp wave activity 1-2 hertz – late non-specific finding

CJD - 14-3-3 protein from CSF – PPV:94.7% NPV: 92.4% values much lower in “non-classic CJD”. Not considered a “confirmatory” test but “supportive”

Grading Criteria for CJD diagnosis

1. Definite CJD - Characteristic neuropath findings and protease resistant prion protein on Western blot
2. Probable CJD - Progressive dementia, characteristic EEG (1-Hz periodic epileptiform discharges), 14-3-3 protein in CSF, 2 or more: myoclonus, visual impairment, EPS-PS, or akinetic mutism
3. Possible CJD - Progressive dementia, atypical EEG, no 14-3-3 protein in CSF, and 2 or more of: myoclonus, visual impairment, cerebellar signs, EPS-PS, or akinetic mutism. Duration less than 2 years.
Creutzfeldt-Jakob Disease

Four Types of Creutzfeldt-Jakob Disease

- Sporadic or sporadic (sCJD): The most common form of Creutzfeldt-Jakob Disease, sporadic CJD occurs in an unexplained manner, and accounts for about 85% of the cases. The disease is shorter than in other forms, and predominantly affects adults aged 50+

- Variant (vCJD): Caused by a genetic mutation, variant CJD accounts for fewer than 5% of all Creutzfeldt-Jakob disease cases. The age of onset can be younger than for sporadic CJD, and the course of illness is generally longer.

- Fatal familial insomnia (FFI): Inherited in an autosomal dominant manner, FFI is a rare form of prion disease characterized by sleep disturbances, memory problems, and eventually premature death.

- Gerstmann-Sträussler-Scheinker (GSS): A rare, inherited prion disease characterized by progressive cognitive decline, movement disorders, and early death.

New Guinea - KURU

- New Guinea thought sparsely inhabited – the Australian government sent patrols to explore their part of the island
- Hundreds of tribes found – 300 languages
- One tribe (the Fore) “took” to the patrol officers – they were very “accommodating”
- Primitive: grass skirts, feathers, no idea they lived on an island
- Always warring with other tribes
- Patrol officers suspected “secrets” about the Fore:
  - Few women and many unmarried men
  - Many deaths – abdominal complaints, shaking/shivering, rapid progression to death
- 1953 a young girl was observed shaking and spasmodically jerking her head from side-to-side. The tribe called it sorcery.

New Guinea - KURU

- 1957 – Enter 33 y/o researcher Carlton Gajdusek (Harvard Med-Peds), Linus Pauling’s lab, trained by 3 Nobel Prize winners
- Rather than “bench” research he wanted to work with “the sick” in “wild places”
- Heard about Kuru, went to New Guinea without permission and refused to leave.
- In months had 41 cases – F:M ratio 14:1 – working with Dr. Michael Alpers
- He essentially lived with the Fore and cared for them earning their trust
New Guinea - KURU

- Gajdusek studied every aspect of Fore society & Alpers filmed their work – they heard rumors of funereal cannibalism but could not prove it
- They eventually acquired diseased brain tissue to send back for study (NIH vs. Australian government)
- Igor Klatzo at NIH reported that the disease was a neurodegenerative disease like CJD
- Gajdusek wanted no part of a “team approach” i.e., the NIH approach. Left New Guinea for the NIH in 1958
- It was around this time that 2 missionaries made a startling discovery: the Fore tribe were found to be eating dead tribesmen in a ritual ceremony (neural tissue given selectively to women and children).
- The Fore (always eager to please) stopped eating their dead at the missionaries’ request and child Kuru deaths stopped.

New Guinea - KURU

- Around this same time American veterinarians visited the UK to investigate an unrelated scrapie outbreak
- William Hadlow (a veterinary pathologist) went to the UK and while there he saw an exhibit of Gajdusek’s Kuru brain pathology – he thought it looked just like scrapie and suggested that someone attempt transmission to an animal host
- He published this idea in the Lancet and sent a copy of it to Gajdusek (who was very upset)

Carlton Gajdusek – Slow Virus

Others already knew that scrapie could be induced by injection of diseased tissue into sheep’s brain and immediately set about setting up a primate vivarium in the US to see if they could cause Kuru by injection of tissue into brain. Gadusek and these men promptly acquired fresh tissue and set up a primate vivarium.

Carlton Gajdusek’s idea was right – his chimps got sick… but 18 months later.
- The disease was terrible with loss of higher function first; with the primates eventually shivering and immobile; finally dragging themselves, mouth to the ground to their food, still turning toward their name until the end (very hard on the caretakers).
- It became clear that the spongiform pathology of CJD, Kuru, and scrapie all looked the same and some were infectious.
- In 1976 he received the Nobel Prize for physiology or medicine for the “Slow Virus”
The work of multiple researchers set upon ways of destroying the infectious nature of this “slow virus.”

The usual anti-infectious agents would not render the agent harmless— including UV radiation or proteolysis. If a virus is “bad news (DNA) wrapped in [somebody else’s protein]” (Sir Peter Medawar) . . . what of this?

As work progressed on the agent causing these diseases the conclusion became clear:

Francis Crick...

There was plenty of abnormal protein found in infected brains - but no abnormal DNA!

1967 – J.S. GRIFFITH - Mathematician

Nature – based on Tikvah Alper’s (South Africa) observations. Proposed that under certain circumstances proteins might be able to self-replicate. “There are at least three distinct ways in which protein self-replication could occur. Protein could switch on a damaging reaction in the host that is normally off. Scrapie agent might be an aberrant form of protein that spontaneously got made, and could serve as a template to induce production of more aberrant forms. Third – might be a protein that takes on a diseased form when it passes in to another animal.

Tikvah Alper

In 1960s studied the infectivity of the scrapie agent. She found that UV radiation had no effect suggesting DNA was not involved. She did not conceive of an infectious protein. But her work altered the perceptions of those that followed.

An Infectious Protein?

• The idea of an infectious self-replicating protein was first addressed in JS Griffith’s 1966 article in Nature
• Stanley Prusiner, MD from UCSF is the individual now most associated with infectious protein disease.
• He claims he saw a CJD pt. as a Neurology resident and was convinced that the cause was an infectious protein (?) His ideas were initially rejected.
• In collaboration with Wm. Hadlow he found hamsters get sick faster after diseased tissue injection and produced more particles – a better/faster model for his “protein” disease.
In 1983 Patricia Merz (electron microscopy) noted SAF (scrapie associated fibrils) in scrapie and CJD. Later that same year someone named Prusiner reported the same structure calling them “prion rods”.

**An Infectious Protein – a Prion**
- Between 1975 and 2012 Prusiner received $131.7 million NIH dollars for his research.
- He “proved” proteases reduced infectivity and DNA dissolvers did not.
- He produced article after article (more than 300 manuscripts by report).
- He named the particle “Prion” (small proteinaceous infectious particle; others suggest the “P-R” in Prusiner had something to do with it).
- In 1997 he received the Nobel Prize.

- It should be noted that Prusiner and Gajdusek knew each other and interacted.
- Prusiner visited the Fore village more than once – and was roundly mocked for his inability to keep up while hiking.
- Prusiner and Gajdusek are reported to have had a fireside chat about the possible proteinaceous nature of prions. They decided to wait until more information was available.
- Instead, Prusiner “stretched” the available results and declared prions infectious proteins in the literature.
- It is said he had nothing to lose…

Prions are conceived as “misfolded” proteins (distorted from proteins that are normally expressed in all cells, especially neural tissue) and then “flipped” into a stable (rigid?) conformation that can cause other proteins to “flip” on contact (a post-translational event).

**Controversy**
- The protein-only hypothesis is widely accepted.
- Multi-component theory (Ohio State – prions created from a mélange of ingredients).
- Heavy metal poisoning.
- The “viral” hypothesis – there must be some DNA/RNA somewhere…
Interesting Sidelights

• When Gajdusek heard Prusiner had won the Nobel Prize he called Prusiner’s work “derivative” and suggested that he had already won the Nobel for the same discovery.

• At the time he found out about the Prusiner award Gajdusek was in prison for child molestation (it turned out that he had as many as 56 pre-teen boys live with him over the years – not counting those in the jungles of New Guinea)

• Prusiner reportedly does not work and play well with others – he is despised by many. The UK would not ask his help early in the BSE epidemic because of his personality

• An unidentified post-doc from his lab reported that at his exit-interview Prusiner told him to stay out of the prion field or he (Prusiner) would “ruin him”.

Prusiner Quotes

• When asked about credit for earlier scientist's contributions to the field. He said: “…repeat and expand (the work) and the original work will never be cited again”.

• When told that “prion” was an already existing word – a flightless bird in the South Seas, he said that he had recently looked up the word in the dictionary to see if his definition was #1. He found that the bird definition was gone. It is reported that he said, “I think it’s extinct!” with great delight.

• Prusiner says prion is pronounced “pree-on”. It is rumored that the British pronounce it “pry-on” just to piss him off.

“History…read it and weep!”

A reading from the Book of Bokonon (p 252)

What prion researchers lacked was a real-life application to promote prions from a medical curiosity to a medical necessity - i.e., money and prestige...enter BSE!

Bovine Spongiform Encephalopathy

• The protein that beef cattle eat is ingested and stays with them as muscle/meat.

• Milk cows have a constant protein-drain as they are milked continuously – thus, protein supplements are necessary to maintain a productive dairy herd

• Those protein supplements came from many sources including abattoir offal – those animal parts that man would not eat.

• Poorly productive dairy cows are slaughtered

• Thus, cattle “parts” were being crushed, rendered, dried and fed back to other cattle as protein cakes.

• Cattle are by nature herbivores.
Bovine Spongiform Encephalopathy

- The first “mad cow” was recognized in 1983. Computerized farming methods noted ongoing weight loss and the cow was sent to slaughter.
- Symptoms: trembling, clumsy walking*, and falling down. When the cows got up, they stood unsteadily shifting weight from one foot to the other. Eventually, they would collapse and die.
- These cows looked a lot like scrapie sheep – anxious, licking themselves neurotically, smacking their lips, and holding their head in a funny position* (sound familiar?)
- Since the symptoms predicted death, these cows were sent to slaughter early in their disease to avoid monetary loss.

A Perfect Storm

- The ongoing “breeding in-and-in” for centuries was a set up for a genetically homogenous herd
- Sick cattle were being sent to the slaughter house earlier to prevent monetary loss for the farmer and were not being examined.
- Cattle were being fed abattoir offal as protein supplement with cow parts
- The “rendering process” temperature had been recently lowered (to make it faster and cheaper)
- Those in charge of investigations did not want to create problems for their superiors
- The national agencies in charge of beef did not want to create a panic that would endanger the economics of beef production
- No one thought that the problem was a danger to humans

First noted 1985 - Carol Richardson’s path report is unequivocal. No action was taken. Ignorance or economics?

BSE and UK Intervention

- SBO ban
- MBM ban
- First verified case of BSE
- Food ban introduced
- Food security assured
- Treatment
Variant CJD

The first documented case of BSE in a human was in 1994 – Stephen Churchill – age 19 years.

Reports of the pathology indicated spongiform change and spectacular amyloid plaques “almost visible to the naked eye”.

The pathology was so severe and different that a new name was assigned to it: (new) variant CJD (vCJD)

A human epidemic was feared.

---

**Variant CJD**

- In the end Europe banned British beef
- The British public wanted all 11 million UK cattle killed (in the end 3.3 million older cattle were slaughtered)
- Examination of beef lymphoid tissue suggested that thousands of humans were exposed to the BSE prion
- Current thru 2009 there have been 173-176 UK deaths from vCJD (definite + probable)
- The vCJD epidemic is thought to have peaked but the possibility of mid-life onset of a more “classic” CJD remains a threat

**vCJD – Other Aspects**

- It appears that the vCJD epidemic has been limited by the fact that there is a genetic propensity involved in getting the disease from prion exposure.
- Virtually every case of vCJD in the UK has possessed the homozygous substitution state at codon 129 for methionine. Those with a valine at the critical site do not appear to be susceptible. Only a minority of the population of the UK are homozygous methionine.
- Recently, an older UK pt. with vCJD (homozygote)
- The Japanese problem...
- Finally, Prusiner’s antibody = $money$ – testing of cattle for BSE
vCJD – Early Treatments

• Quinacrine – a poor anti-malarial. 2 researchers showed that it reduced the infectivity of the prion particle. In the 1st patient treated she improved markedly but drug-induced liver toxicity forced the stoppage of the drug. She was dead in 6 months. The BMRC is now in a phase II trial assessing quinacrine usefulness.

• Pentosan – A drug originally used for interstitial cystitis. A beechwood derivative. It appears to arrest the disease in humans but improvement has not been seen. It is thought to block the attachment site for the abnormal conformer of prion protein. Not thought promising although drugs of a similar mechanism might be.

vCJD – Should We Be Worried?

• In 1989 Elias and Laura Manuelidis (Yale) looked at pathology of 46 American brains from patients with Alzheimer Disease on their death certificate – 6 had CJD.

• 35 million cattle slaughtered/year in USA
• USDA tests 40K for BSE (detects at BSE 1/1M)
• 195K “downer cows”/year are restricted from human consumption (at least the ones we know about).
• In 2004 one meat company (Creekstone Farms) volunteered to test all cattle for BSE – the USDA declined to give them testing kits
• Safety or economics?

The Venetian Curse

• After years of anxiety and embarrassment about the family curse (followed by the expected death) a female family member married an Internist (Ignazio Roiter).
• After hearing the tale of insomnia and death he finally met a family member with the illness and witnessed modern medicine’s abject failure in diagnosis for himself.
• After researching family archives he sought out the famed Italian sleep researcher Elio Lugaresi.
• The sleeping EEG showed an awake state with delta waves (a finding c/w encephalopathy)
• In the end – no sleep but periods that looked like REM sleep without paralysis
• Lugaresi called it “Fatal Familial Insomnia”
• Autosomal dominant inheritance

Fatal Familial Insomnia

• The brain was sent to Gambetti at Case Western – normal brain with spongiform gaps and astrocytes in the hypothalamus.
• In 1986 Lugaresi & Gambetti published their findings (NEJOM 315:997-1005)
• Later they enlisted Prusiner to test the FFI brains – all positive by antibody for prion dz.
• Gambetti now has a genetic test for FFI – PrP (codon 129-meth / codon 178-asn)
• Not surprisingly, not all family members want the test
• Only about 40 families in the world are afflicted with FFI
TSE - Iatrogenic transmission

- PrPSc is not denatured by usual methods of sterilization
- It survives incineration and bonds to metallic surgical instruments.
- It has been transmitted during surgical procedures in 2 documented cases (a deep brain electrode).
- BSE PrP is thought to make its way to the bovine CNS thru the lymphoid tissue of Waldeyer’s ring – UK human exposure was calculated by looking at bovine tonsillar tissue.
- Human tonsillar tissue is of low infectivity but may contain PrPSc – Currently the UK has changed to disposable instruments for T&A.
- Some US hospitals now decline to do brain biopsy for CJD.
- Restriction for blood transfusion are also in force (WBCs).

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Parkinson’s disease is characterized by abundant neurons in the substantia nigra, the medial base of the caudate nucleus, and the neocortex of middle dopaminergic neurons. However, a case is reported that shows a relationship between synuclein formation and neurodegeneration in the striatum. Here, we found that in zebrafish, neurons with single lateral extensions of a single α-synucleinacious cell are able to form a predictable pattern of neurodegeneration. The pathology was also observed in the substantia nigra, the parkinsonian lesion area, and was accompanied by reduced dopamine levels in the midbrain. This model of α-synuclein transmission establishes a mechanism link between transgenic and nontransgenic models of Parkinson’s disease.

NEUROLOGY TODAY

Amyloid Beta Aggregates in Alzheimer’s Disease Are Prions, Study Finds

Other Protein Misfold Diseases

- Alzheimer Disease
  - Tau protein & beta-amyloid
- Parkinson Disease
  - Tau protein & alpha-synuclein
- Huntington Disease
  - Huntingtin protein (poly-Q repeat - glutamine)
- Amyotrophic Lateral Sclerosis
  - Mutated superoxide dismutase / TDP-43 / FUS-TLS

Monoclonal Antibody Therapy

- Human monoclonal Ab are in Phase II&III trials against B-amyloid and alpha-synuclein.
- Bapineuzumab (4 Phase III), Solanezumab (2 Phase III), Aducanumb (2 Phase III).
- For most effect is dose-dependent.
- Higher dose associated with more rapid reduction of prion and the occurrence of micro-hemorrhage and headache.
- Aducanumab reduced cognitive decline compared to untreated controls (J Sevigny, et al. Nature 2016; 537 (7618) ... still no proof it alters progression.

LETTER

Sustained translational repression by eIF2α-P mediates prion neurodegeneration

- Methionine-129 more likely to for amyloid fibrils.
- Homozygous M-129 increases risk of Alzheimer dementia at an earlier age.

Neurology July 27, 2004 vol. 63 no. 2 364-366
Phage M13

• Single stranded DNA phage – infects certain strains of E. coli
• Using the phage as a vector for gene delivery it was accidentally found that the phage disaggregates alpha-synuclein
• When incubated with amyloid fibers the phage bound only fibers (not monomers) and disaggregated them.
• Adequately purifying phage was problematic. So…

The G3P minor coat protein produced the same effect (albeit at reduced efficiency) but the protein could be made in huge pure quantities using a recombinant approach and binding it to immunoglobulin.

Animal and Human Prion Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism of pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somic (Kuru people)</td>
<td>Infection through stavolite contamination</td>
</tr>
<tr>
<td>Geratropic Creutzfeldt-Jakob disease</td>
<td>Infection from prion-converted VCF, then more prions, and so forth</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease</td>
<td>Infection from scrapies prion</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease</td>
<td>Geratropic infection in P19 gene</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Geratropic infection in P19 gene</td>
</tr>
<tr>
<td>sporadic Creutzfeldt-Jakob disease</td>
<td>Geratropic contamination by ingestion of beef infected with scrapies prion</td>
</tr>
</tbody>
</table>

“Beware the man who works hard to learn something, learns it and finds himself no wiser than before. He is full of murderous resentment of people who are ignorant without having come by their ignorance the hard way.”

A reading from the Book of Bokonon (Cat’s Cradle p 281)
Kurt Vonnegut
Tiger got to hunt,
Bird got to fly;
Man got to sit and wonder, “Why, why, why?”
Tiger got to sleep,
Bird got to land;
Man got to tell himself he understand.

From the Book of Bokonon

“And so it goes…wouldn’t ya’ know”