And They’re Not Going To Take It Anymore

L. Tuck Foree, Jr.
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What is making the cows mad?

- **Bovine Spongiform Encephalopathy (BSE)**
  - Literally means “Spongy Cow Brain”
- Member of the TSE Family
  - Scrapie
  - CJD
- Slow acting
- Formation of plaques in brain
- Acute dementia
- Eventual bovine death
- Literally a crazy cow
- First known case of BSE
What is the Public Perception?

**HUMAN CASES**
Most victims so far are British. But France and Ireland have had a few.

*Figures include still-living persons with probable vCJD or deceased persons whose diagnoses have not yet been confirmed.*
The realities of BSE:

- No known human link
- Only five cases with “Unknown Circumstances”
- But, there is a similar human disease:
  - Cruetzfeldt-Jacob disease
- Caused by a prion

Why Worry about it?

- Spread to America would decimate the entire meat industry
- A terrible consequence:
### Epidemiology of Mad Cows

#### Number of Reported Cases of BSE Worldwide in Animals*

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>22</td>
</tr>
<tr>
<td>Denmark</td>
<td>3</td>
</tr>
<tr>
<td>France</td>
<td>245</td>
</tr>
<tr>
<td>Germany</td>
<td>35</td>
</tr>
<tr>
<td>Great Britain</td>
<td>177,695</td>
</tr>
<tr>
<td>Ireland</td>
<td>587</td>
</tr>
<tr>
<td>Italy</td>
<td>2</td>
</tr>
<tr>
<td>Lichtenstein</td>
<td>2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>1</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>9</td>
</tr>
<tr>
<td>Portugal</td>
<td>509</td>
</tr>
<tr>
<td>Spain</td>
<td>17</td>
</tr>
<tr>
<td>Switzerland</td>
<td>367</td>
</tr>
</tbody>
</table>


Sources: U.K. Ministry of Agriculture, Fisheries, and Food; Office International des Epizooties
Prions: Stanley Prusiner, UCSF

1995: “Proteinaceous Infectious Particles”

Not Taken Well

Proved his theories with several studies

- Resistance to radiation
- Absence of viral genome
- Knockout mice without resident protein gene survive

BSE is a prion
Transmissible Spongiform Encephalopathies

- Most common form of Prion disease
- Variants in species
  - BSE: Cows
  - Scrapie: Sheep, Hamsters
  - Chronic Wasting Disease: Deer, Elk
  - Feline Spongiform Encephalopathy: Cats
  - CJD: Humans
  - Variant CJD (vCJD): Possible BSE link in humans
  - Kuru: Humans

- Characterized by protein plaques
- Many different pathways of infection
# Existing Prion Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism of pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Kuru (Fore people)</td>
<td>Infection through ritualistic cannibalism</td>
</tr>
<tr>
<td>Iatrogenic Creutzfeldt-Jakob disease</td>
<td>Infection from prion-contaminated HGH, dura mater grafts, and so forth</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease</td>
<td>Infection from bovine prions?</td>
</tr>
<tr>
<td>Familial Creutzfeldt-Jakob disease</td>
<td>Germline mutations in PrP gene</td>
</tr>
<tr>
<td>Gerstmann-Straussler-Scheinker disease</td>
<td>Germline mutations in PrP gene</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Germline mutation in PrP gene (D178N and M129)</td>
</tr>
<tr>
<td>Sporadic Creutzfeldt-Jakob disease</td>
<td>Somatic mutation or spontaneous conversion of PrP⁰ into PrP⁰⁰⁰⁰⁰²⁰²⁰</td>
</tr>
<tr>
<td><strong>Animal diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Scrapie (sheep)</td>
<td>Infection in genetically susceptible sheep</td>
</tr>
<tr>
<td>Bovine spongiform encephalopathy (cattle)</td>
<td>Infection with prion-contaminated MBM</td>
</tr>
<tr>
<td>Transmissible mink encephalopathy (mink)</td>
<td>Infection with prions from sheep or cattle</td>
</tr>
<tr>
<td>Chronic wasting disease (mule deer, elk)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Feline spongiform encephalopathy (cats)</td>
<td>Infection with prion-contaminated MBM</td>
</tr>
<tr>
<td>Exotic ungulate encephalopathy (greater kudu, nyala, oryx)</td>
<td>Infection with prion-contaminated MBM</td>
</tr>
</tbody>
</table>
Spongy Brains:

A: Mouse Inoculated with FFI
B: Mouse Inoculated with fCJD

High Aggregation of Prions
What is the Mad Prion?

- PrP<sup>C</sup>
- Resident in brain
- No known function
- Nearly all mammals
- Knock-out mice without PrP<sup>C</sup> gene live without it
- Infectious prion: PrP<sup>Sc</sup>
What is the Mad prion? (con’t)

PrPC is primarily α-helical

PrPSc has β-sheet domains with hydrophobic residues facing out

Hydrophobic residues create insolubility in brain tissue
Recruitment of Mad Prions

Two Theories of Prion Recruitment

**Template Assistance Mechanism**

\[ \text{PrP}^\text{Sc} \text{ Monomer} + \text{PrP}^\text{C} \text{ Monomer} \rightarrow \text{PrP}^\text{C}-\text{PrP}^\text{Sc} \text{ Heretodimer} \rightarrow \text{Conversion} \rightarrow \text{PrP}^\text{Sc} \text{ Homodimer} \rightarrow \text{PrP}^\text{Sc} \text{ Monomer} + \text{PrP}^\text{Sc} \text{ Monomer} \]

**Nucleated Polymerization Mechanism**

\[ \text{PrP}^\text{Sc} \text{ Oligomer} + \text{PrP}^\text{C} \text{ Monomer} \rightarrow \text{PrP}^\text{C}-\text{PrP}^\text{Sc} \text{ Oligomer} \rightarrow \text{Conversion} \rightarrow \text{PrP}^\text{Sc} \text{ Oligomer} \]

Note: PrPSc; Infectious Prion  PrPC; Normal Form
How do the Cows get Mad?

Meat and Bone Meal (MBM)
- Cow Carcasses used as cattle feed
- Outlawed in all of Europe

Cows, in England, Contract BSE

BSE infected cows die and are incorporated into MBM.

Cows that eat the MBM contract BSE
How can you Tell When your Cow is Mad?

- Currently, Testing by Microscope investigation:

- Current testing requires nearly 12 months
- New Western Blot testing is showing promise
Western Blot Analysis

- Measures prion protein in clearance studies
- Prions are isolated from diseased tissue
- Prions are then compared to serial dilutions on a Western Blot
- Testing takes approximately two weeks
Possible Treatment

- Treatment with Amphotericin B (AmB) or MS-8209
- AmB has shown to slow TSE

Hypothesis:
- AmB associates with sterols in the membrane
- Disrupted membrane hinders PrP attachment

Or: AmB may directly affect PrP conversion

Studies now being performed on model prion systems
- Insulin fibrils
The Future of Mad Cows

- Establishing the presence any interspecies link
- Further research on treatment
- Making it safe to eat meat everywhere
References

- Cowley, Geoffrey. Cannibals to Cows: The Path of a Deadly Disease, *Newsweek*. March 12, 20001
- Interview with Kristy Osborne, Graduate Student of Speech and Hearing Pathology