

Prion Diseases : The New Plague?

A little history and mystery... Scrapie

- ◆ First prion disease recognized over 300 years ago in England
- ◆ Affected sheep
- ◆ Was present in Central Europe well before it spread to England
- ◆ Agent was unknown
- ◆ Endemic in sheep by the early 20th century
- ◆ Not spread to humans
- ◆ 1930's... agent shown to be transmissible to other sheep- still no clue about the agent

Signs and Symptoms:

- ◆ Intense itching alleviated by rubbing against walls, trees etc.
- ◆ Rubbed off wool
- ◆ Tremors, staggers, blindness
- ◆ Always fatal



A sheep with scrapie...

A little history and mystery... Kuru

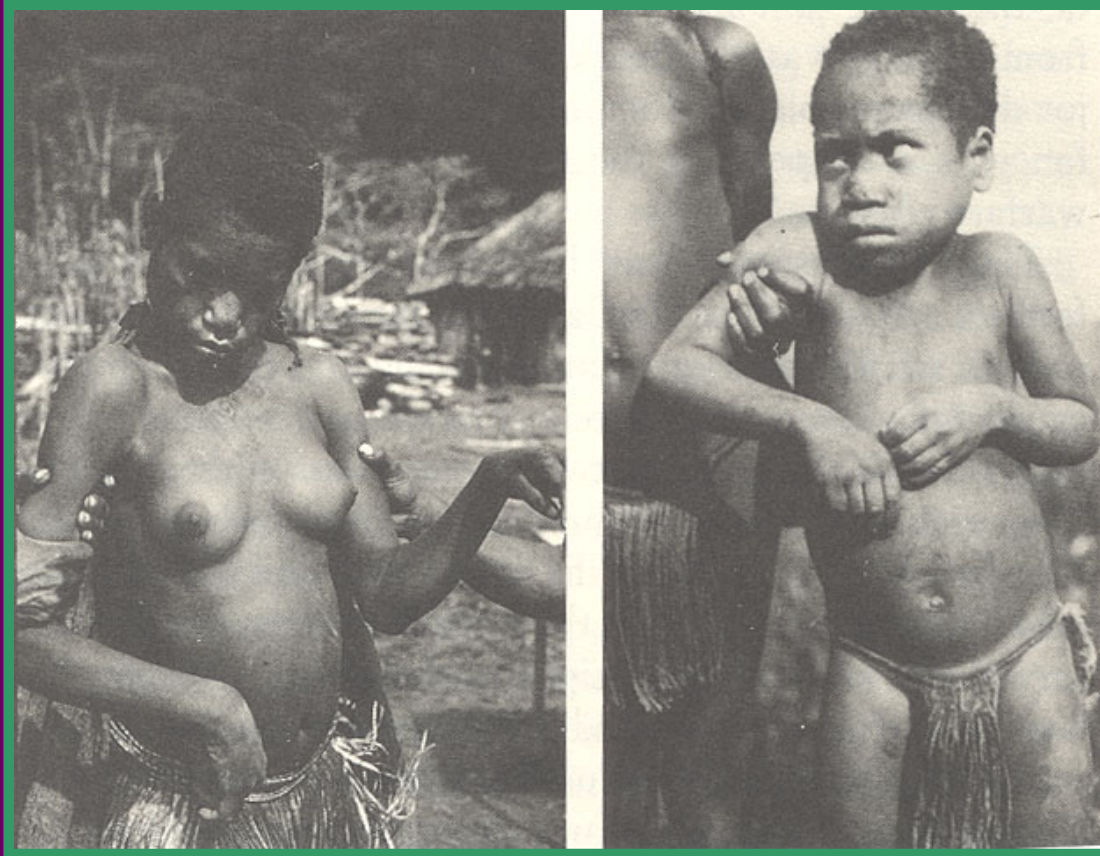
Kuru- affected the Fore tribe of New Guinea



Kuru means shivering or shaking

- ◆ The Fore tribe practiced ritualistic cannibalism
- ◆ This wasn't an ancient practice among the Fore- the idea came from other tribes in the region
- ◆ Ate those that died of other causes- did not kill humans for food
- ◆ Idea of burying dead tribesmen seemed like a waste of food
- ◆ Those that were dying assigned others the parts they would eat...
- ◆ Men got the choice cuts- as it were
- ◆ Women got the leftovers... brain, organs etc.
- ◆ Women and children prepared the bodies for the feasts

After the practice of cannibalism began, a strange disease began to afflict the Fore- mainly the women and the children.



Two victims of Kuru

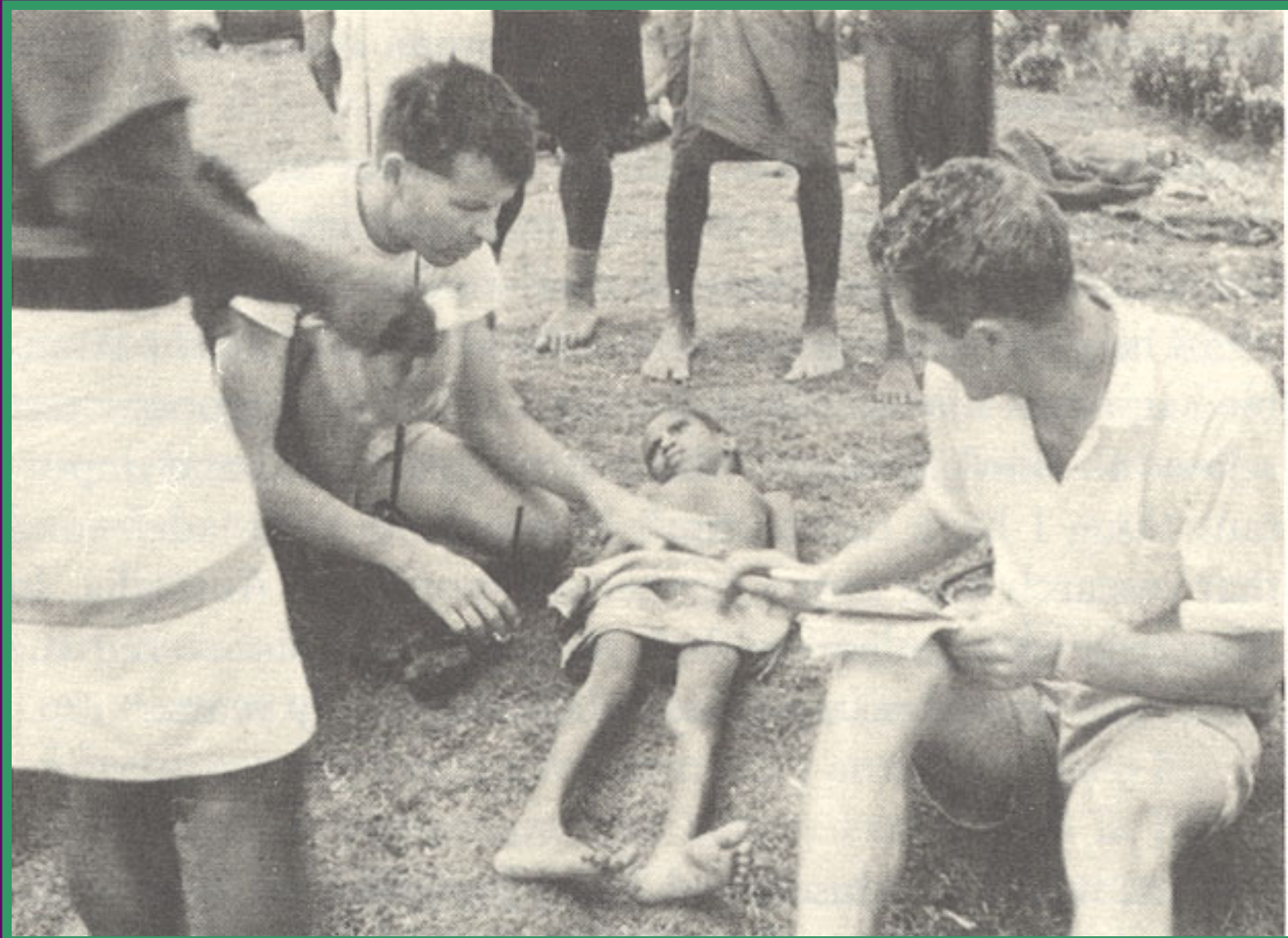
The deaths were thought to be by sorcery- practiced by the men on the women - so the cannibalism continued...

Signs and symptoms:

Classic Kuru...

- ◆ Month One- Trouble walking- usually need a cane
- ◆ Month Two- Tremors, involuntary muscle contractions, difficulty speaking
- ◆ Month Three- almost total incapacitation
- ◆ Months 4-12- Incapacitated- can't walk, swallow etc., but remain completely aware almost until the end when dementia sets in
- ◆ Always fatal- usually in 1 year or less

- ◆ In 1957, Dr. Carleton Gajdusek was asked by Vincent Zigas to help study the disease afflicting Fore women and children
- ◆ Zigas thought the disease was a type of encephalitis
- ◆ Classic infectious agents cause inflammation in a patient... this disease caused none
- ◆ It was noted that the disease appeared similar to a condition called Creutzfeldt-Jakob disease (CJD)
- ◆ A veterinarian, Bill Hadlow that was studying scrapie also noted its similarity to Kuru both in physical symptoms and brain pathology
- ◆ Stopping cannibalism has stopped the spread of Kuru- non-existent now



Gajdesuk and Zigas examine a boy in the late stages of Kuru- The child is nearly incapacitated

Other Scrapie/ Kuru like Diseases

Transmissible Mink Encephalopathy (TME)

Feline Spongiform Encephalopathy (FSE)

Bovine Spongiform Encephalopathy (BSE)

Chronic Wasting Disease (deer & elk) (CWD)

Creutzfeldt- Jakob Disease (CJD)- also variant CJD, sporadic CJD, familial CJD

Fatal Familial Insomnia

Gerstmann-Straussler Scheinker Disease

What causes these diseases?

1) Gajdusek and others showed that the disease agent is transmissible and proposed that it is not a virus or other known type of infectious agent

2) A protocol for partial purification of agent from hamsters infected with scrapie agent showed that a protein required for infection

3) Tried various methods to inactivate agent by destroying DNA/RNA

4) No success- so term PRION introduced by Stanley Prusiner

Prion= “small proteinaceous infectious particle which resists inactivation by procedures that modify nucleic acids”

Prusiner had three hypotheses as to the nature of the prion

- 1) A slow virus with nucleic acid protected by a protein... the nucleic acid codes for a protein
- 2) Proteins surrounding a non-coding nucleic acid
- 3) Protein without any associated nucleic acid

Hypothesis 3 was hard to believe...there were NO known infectious agents that caused disease without the presence of nucleic acid (DNA/RNA)

Prusiner believed that the correct hypothesis was #3 but nobody believed him so...

1) He determined part of the protein sequence of the scrapie agent (called PrP^{sc})

2) Used the sequence to develop a probe and located a gene within hamsters (his lab animal of choice) that codes for this protein (called PrP^c)... this means that hamsters produce the same protein that causes scrapie infections in sheep

3) Since this work, scientists have shown that the gene for this protein- PrP^c is found in ~ 50 mammals including humans, great apes, sheep, goats, cattle, wild game, dolphins, whales etc. and is believed to be in all mammals

4) Normal function of the protein is still unknown

Why does the PrP protein cause disease???

◆ PrP can exist in two conformations:

1) Normal cellular (PrP^c) 2) Abnormal (PrP^{sc})

◆ Abnormal PrP arises in a number of ways:

1) The abnormal form of the protein is taken in from outside the body (eaten)

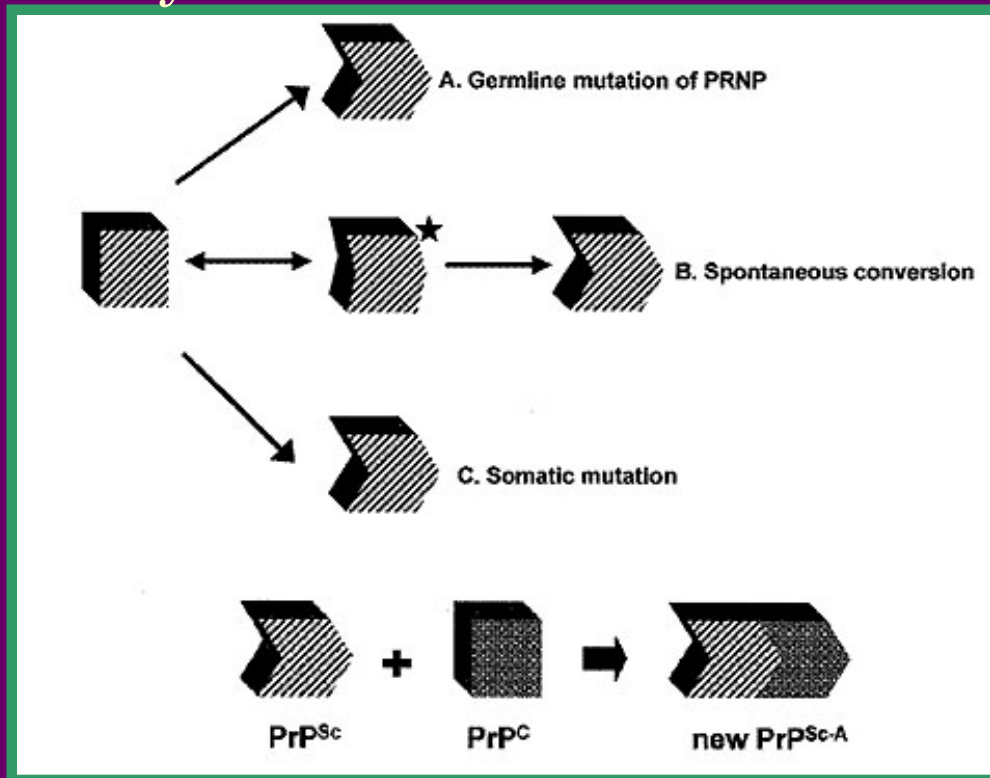
2) An inherited mutation in the gene for PrP causes production of abnormal PrP protein = Familial genetic disorder

3) A change in the PrP gene of an individual (somatic) that leads to abnormal protein production = not inherited

4) Spontaneous conversion of the protein itself

Once an abnormal form of the protein is either produced, consumed, or spontaneously changed, it acts as a template and causes other normal PrP^c protein to change conformation into PrP^{sc}

The PrP^{sc} clumps together and causes holes and plaques in the brain = neurodegenerative symptoms of this family of diseases



Conversion of PrP^c to PrP^{sc}

- ◆ Prusiner's lab figured out that a new type of infectious agent exists...
- ◆ They solved a great medical mystery and performed rather elegant experiments to determine the nature of the agent
- ◆ So why do we care about an infectious agent that causes disease in sheep and in New Guinea cannibals???

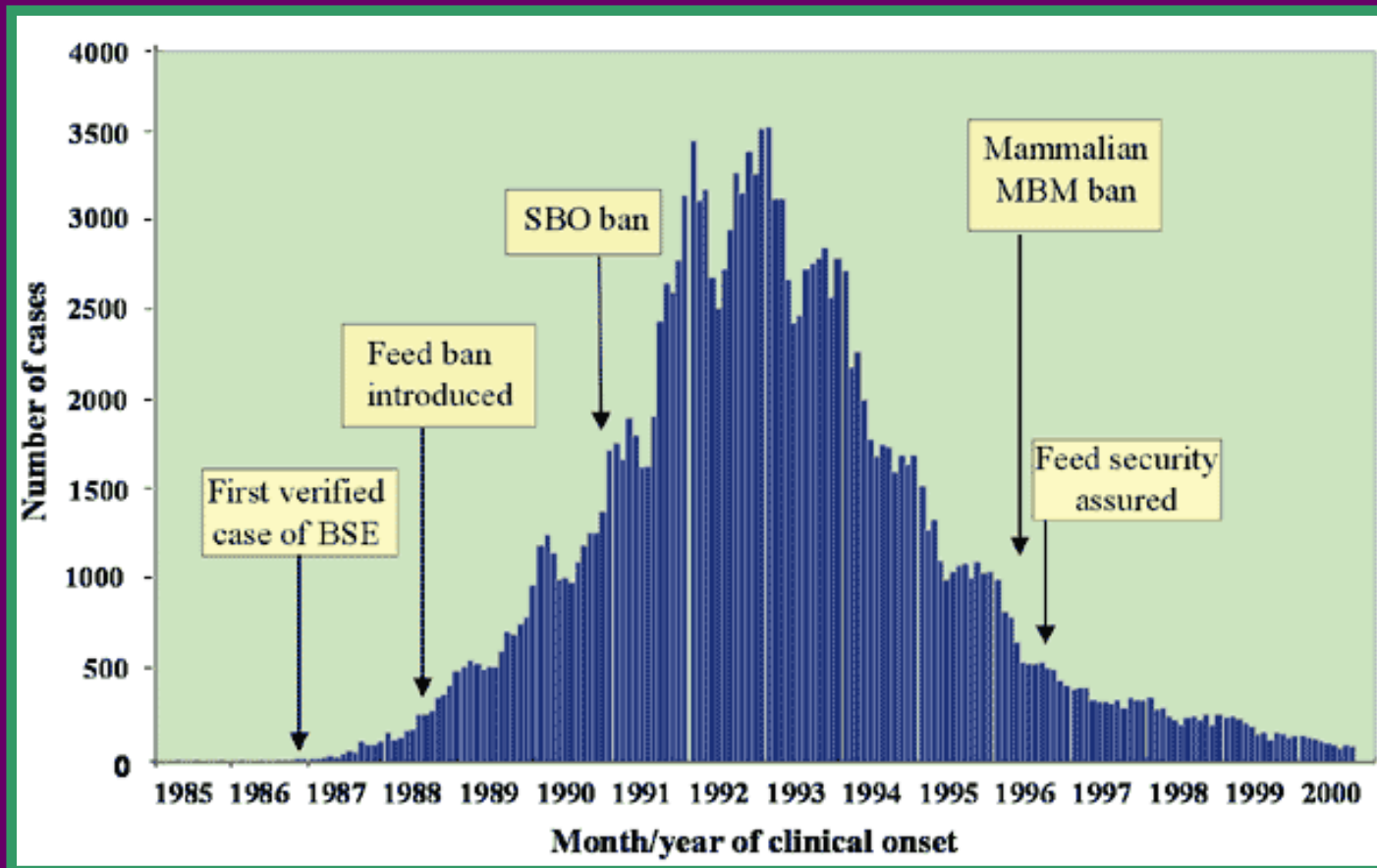
- ◆ Mad Cow Disease...that's why!!

Bovine Spongiform Encephalopathy or Mad Cow Disease - a new disease within the prion family

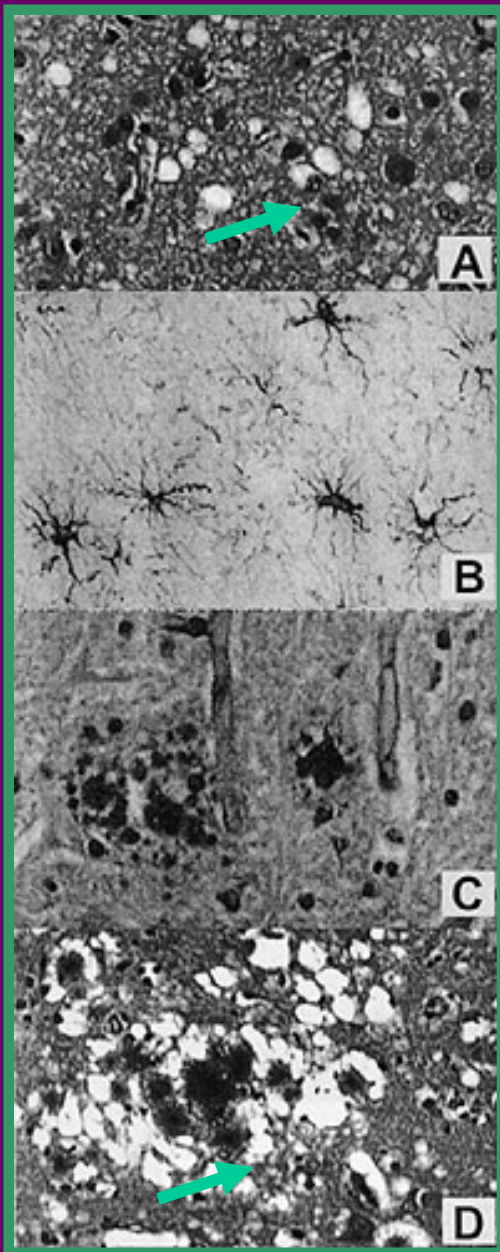
- ◆ Prior to 1986- strange bovine encephalopathies were reported by farmers in England
- ◆ It was assumed that the disease was similar to scrapie and was caused by the practice of feeding cattle protein meal made of unused sheep and cattle carcasses
- ◆ Based on this assumption, the practice of feeding sheep carcasses to cattle was halted, but cattle was still fed to other cattle... cannibals... see a connection here???
- ◆ By 1986, BSE was reported to the public and had reached epidemic proportions
- ◆ 1988- The public was told that eating uninfected animals was safe and all infected animals would be slaughtered

- ◆ Rationale for the 1988 report to the public... BSE is simply a form of scrapie. Scrapie is not infectious to humans so BSE won't infect humans.
- ◆ The public was urged to continue to eat cow brains etc. and the gov't solution to controlling BSE was to stop feeding cattle protein to cattle
- ◆ 1989- recommended that all cattle offal be destroyed. By this time, BSE had been experimentally transmitted to mice, and accidentally transmitted to zoo animals in their feed... and the public kept eating!
- ◆ 1990- media hype about BSE leads to public hysteria, bans on beef in some schools, and a marked drop in beef consumption in England... the year the Minister of Agriculture tries to feed his daughter a burger on TV- she refused to eat it

- ◆ 1991- the gov't still trying to convince public that BSE was not a risk to humans
- ◆ 1992- restrictions on cattle feed imposed in 1988 began to bring the BSE epidemic under control



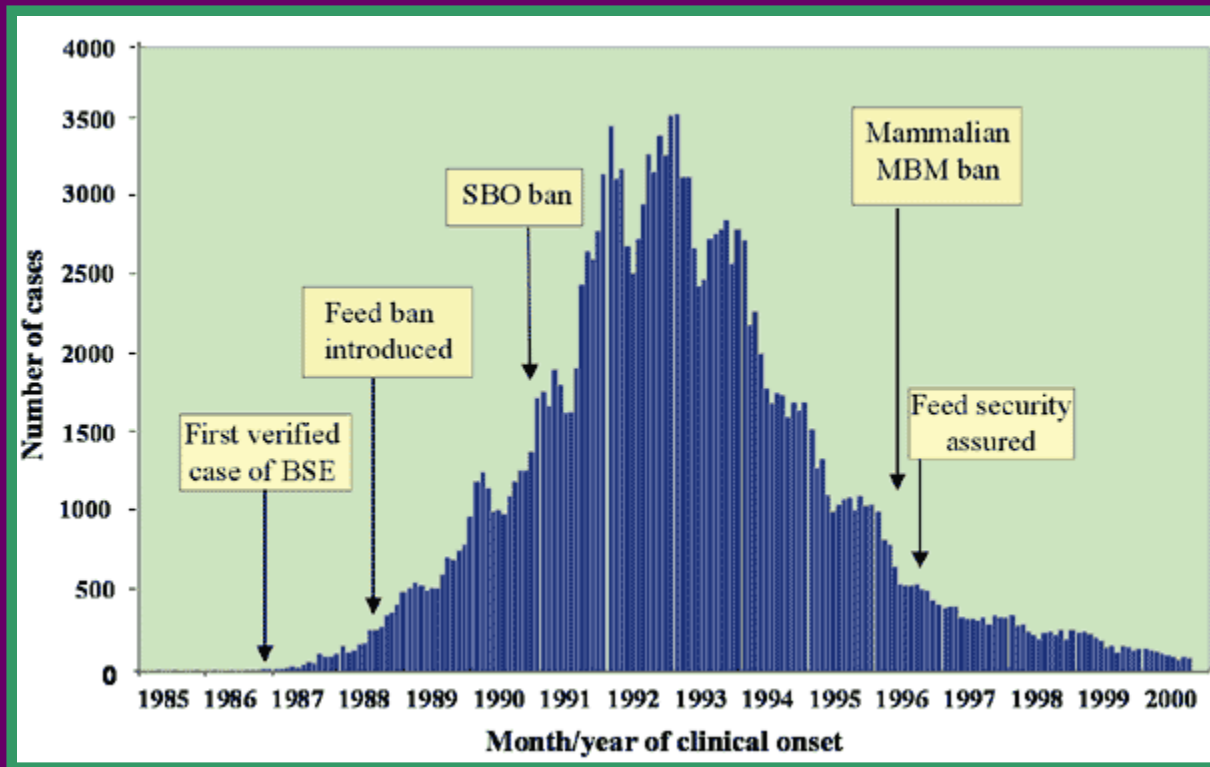
- ◆ Everything seemed fine. BSE was under control. People weren't as concerned because it was only scrapie right?
- ◆ Wrong! In 1995, the incidence of Creutzfeldt- Jacob Disease, a sporadic human spongiform encephalopathy increased. Three cases were reported in patients aged 16, 19, and 29. This is important because most CJD patients are older than 50.
- ◆ By the end of the year, there were 10 probable cases
- ◆ In early 1996, two additional cases emerged
- ◆ None of the cases appeared to be caused by the genetic form of CJD- new disease termed variant CJD
- ◆ 1996- the link established between vCJD and eating contaminated beef



vCJD causes the same sort of plaques and holes in the brain that Kuru, scrapie, BSE, CJD etc.

Mad Cow Predictions- Is the epidemic under control or has it not even really begun??

- ◆ The first case of vCJD occurred in 1994
- ◆ This was almost a decade after the first report of BSE in cattle
- ◆ How long is the incubation period? We don't know. It appears to be long.
- ◆ If it is 5-10 years, then the incidence in humans is probably on the decline.
- ◆ If it is 10-15, then we could possibly have a large outbreak of vCJD within the next few years



First verified BSE case in 1986. First case of vCJD in 1994. Shorter incubation means that we are seeing the maximum number of cases at this time. A long incubation means that people who ate beef during the peak of the BSE epidemic will not show signs of infection until ~ 2004 or so

- ◆ Since we are unsure of the incubation period, the chance of spreading vCJD between humans remains a very real possibility
- ◆ Possible transmission via blood transfusions, organ donation, surgical procedures etc.
- ◆ Abnormal prion protein is very hardy. Doesn't denature easily, can't be inactivated by conventional cooking
- ◆ Basically we just have to wait and see
- ◆ As of November 2000, a total of 87 cases had been reported and there has been a modest increase in the number of cases each year

◆ So if scrapie isn't infectious to humans, and BSE was actually scrapie, how did we get infected??

◆ Prion proteins don't cause infections across species barriers very effectively EXCEPT when the species are closely related.

◆ Sheep and cows are close enough that the scrapie prion was able to infect cattle.

◆ One theory is that the prion was changed enough in the cattle that it was able to cross another species barrier and infect humans

- ◆ For all prion diseases, it looks like they all arose initially by genetic mutations or spontaneous conformational changes = CJD, GSS, FFI, Scrapie
- ◆ These diseases were and are found at low levels everywhere
- ◆ But humans have caused epidemics by (1) importing infected species = scrapie (2) Being cannibals = Kuru (3) Feeding other animal species to themselves = BSE → vCJD (4) Iatrogenic transmission (medical procedures), corneal transplants, cadaver human growth hormone etc.