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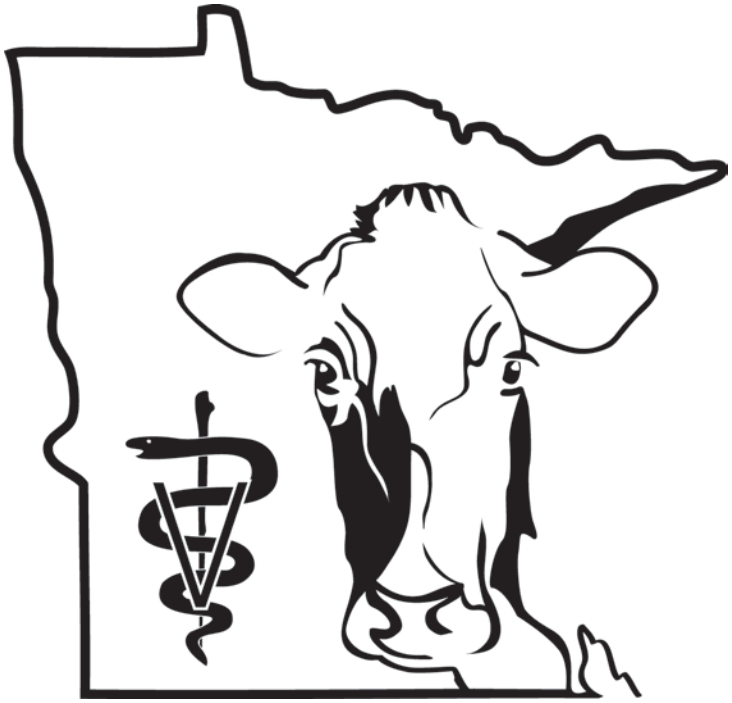

ST. PAUL, MINNESOTA
UNITED STATES OF MINNESOTA

Transmissible Spongiform Encephalopathies (TSE)

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Characteristics of TSE's

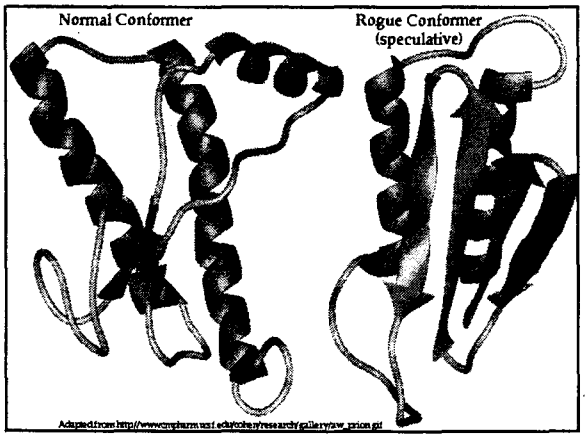
- Prolonged incubation period
- Progressive debilitating neurological disease
- Fatal

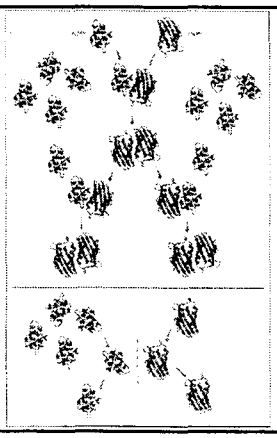
THE INFECTIOUS AGENT

- Likely an "infectious protein" (Prion hypothesis)
- Survives UV radiation and other procedures that destroy nucleic acids
- Elicits no detectable immune or inflammatory response

Prion Hypothesis

- Isoform of normal host cellular protein – transformation of α-helical structure into β-sheet (unfolding and flipping of normal "cellular" confirmation to "scrapie" form)
- Prion accumulates in neural cells disrupting function and leading to vacuolization and death





"SPECIES BARRIER"

- Because of conformational differences between prion proteins in different species, transmission is prevented
- Prion responsible for scrapie differs substantially from the human prion protein which may explain why scrapie has never transferred to humans

JAMA 1999;281:2330-9

Prion Transmissibility

- As a strain of TSE moves from one species to the next it may acquire an altered host range
- Passage of mouse-adapted strains of Scrapie through hamsters altered their transmissibility to rodents
- Human strains of Kuru or CJD did not transmit to ferrets or goats until passed through primates or cats

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES IN ANIMALS

- Scrapie in sheep and goats
- Mink transmissible encephalopathy
- Chronic Wasting Disease of deer and elk
- Bovine Spongiform Encephalopathy

Scrapie

- Non-febrile, fatal, chronic disease of sheep and goats
- Causes pruritus that leads sheep to rub against objects and "scrape" off wool
- Known since early 1700s; seen worldwide
- Recognized in U.S. in 1947
- Transmission – horizontal (placenta), vertical, or environment

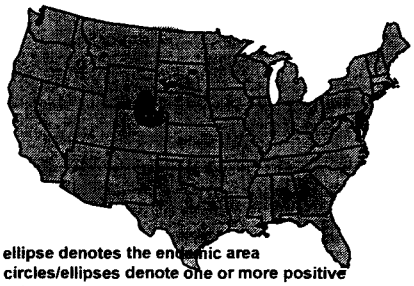
Scrapie

Chronic Wasting Disease (CWD) of Deer and Elk

- First recognized in 1967
- CWD diagnosed from farmed elk
- Confirmed in free-ranging deer and elk in limited counties in CO, WY, and NE
- Affected species: Rocky Mountain elk, mule deer, white-tailed and black-tailed deer
- <200 cases since 1981
- Unknown mode of transmission

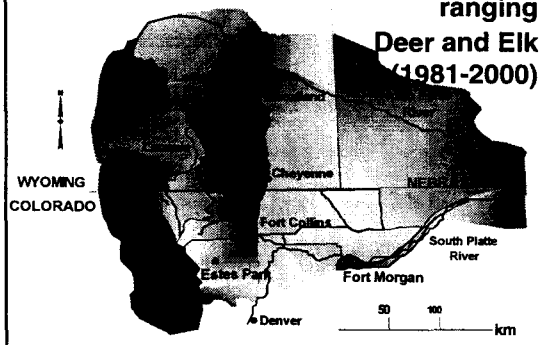
Chronic Wasting Disease

Chronic Wasting Disease - Distribution



*The gray ellipse denotes the endemic area
The black circles/ellipses denote one or more positive captive elk herds

Chronic Wasting Disease in Free-ranging Deer and Elk (1981-2000)



Bovine Spongiform Encephalopathy (BSE)

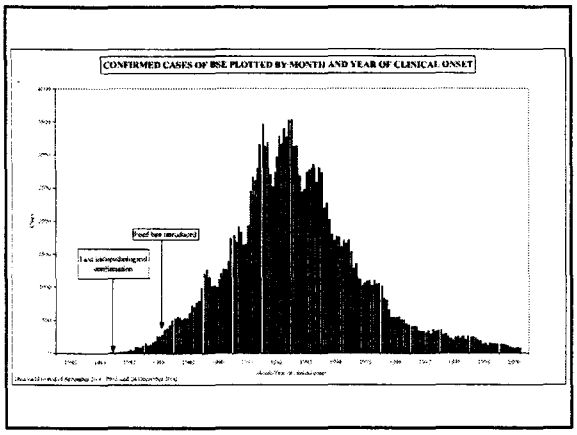
- First diagnosed in 1986 in Great Britain
- Over 95% of all cases have occurred in the United Kingdom
- Associated with ruminant-derived feed
- BSE not documented in the United States

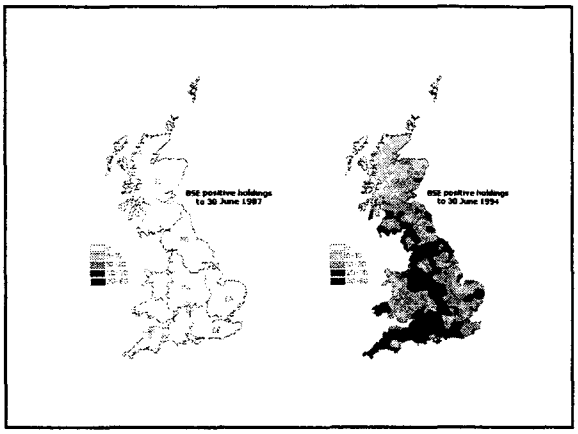
CLINICAL PRESENTATION OF BSE

- Adult cattle 4-5 years of age
- Onset of behavioral changes (aggression or anxious)
- Ataxia (tremors, incoordination)
- Incubation period = 2 to 8 years

BSE OUTSIDE THE UK
(In Native Animals)

- Belgium
- Denmark
- France
- Germany
- Ireland
- Italy
- Liechtenstein
- Luxembourg
- Netherlands
- Portugal
- Spain
- Switzerland





Other Species Affected by BSE

Exposure	Species (No.)
Meat/bone meal	Kudu (6), Gemsbok (1), Nyala (1), Oryx (2), Eland (6), Ankole Cow (2)
Cattle tissues	Domestic cat (70), Cheetah (4), Puma (3), Tiger (1), Ocelot (2)

Why BSE in the UK?

- Large sheep population (make up 14% of rendered protein in the UK vs. 0.6% in the U.S.)
- High rate of endemic Scrapie
- Changes in rendering practices
- Feeding practices (MBM constituted 4-5% of the diet of dairy calves)

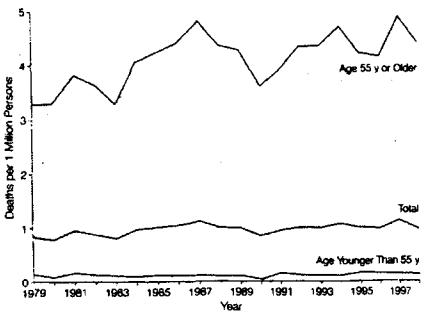
HUMAN TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

- Creutzfeldt-Jakob Disease (CJD)
- Variant Creutzfeldt-Jakob Disease (vCJD)
- Gerstmann-Straussler-Scheinker Syndrome (GSS)
- Kuru
- Fatal Familial Insomnia

CREUTZFELDT-JAKOB DISEASE

- 90% of cases occur sporadically
- 10% occur within families with an autosomal dominant pattern of inheritance
- Less than 1% occur through iatrogenic transmission

Figure. Creutzfeldt-Jakob Disease Age-Adjusted and Age-Specific Death Rates, and Deaths by Age United States, 1979-1998



SOURCES OF IATROGENIC TRANSMISSION OF CJD

- Corneal transplants
- Duramater grafts
- Treatment with cadavar-derived human growth hormone
- Contaminated neurosurgical instruments

Person-to-Person Transmission of Prion Diseases

Mode of Transmission	Example (No. of Cases)	Incubation Period (Yrs)
Intracranial transplantation/inoculation	Dural grafts (>80)	1.3-17
	Inadequately sterilized instruments/electrodes (4)	0.6-2.2
Extracranial transplantation/inoculation	Corneal grafts (2)	1.3-1.5
	Human pituitary growth hormone (>100)	4-19
Extracranial inoculation or oral exposure	Unknown Exposure to BSE (>80)	?
	Transmission of kuru by cannibalism (>2-3000)	4-40

Transmissibility of CJD

- No experimental transmission with any fluid except CSF
- No excess risk for health care workers
- Universal precautions only
- Disposable instruments or 1N sodium hydroxide or undiluted bleach for 1 hour then autoclave at 136° C. for 1 hour

Variant CJD (vCJD)

- In April 1996, the *Lancet* reported 10 CJD cases in the United Kingdom with distinct differences from sporadic "classical" CJD
- These individuals were younger and had different clinical and pathological features from sporadic CJD

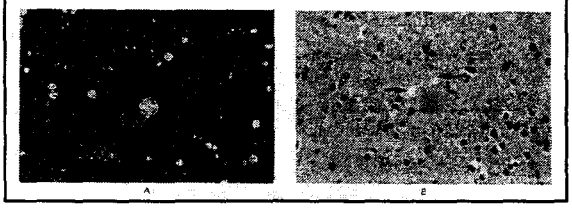
TABLE 5. COMPARISON OF NEW-VARIANT AND SPORADIC CREUTZFELDT–JAKOB DISEASE.

CHARACTERISTIC	NEW VARIANT*	SPORADIC
Mean age at onset (yr)	29	60
Mean duration of disease (mo)	14	5
Most consistent and prominent early signs	Psychiatric abnormalities, sensory symptoms	Dementia, myoclonus
Cerebellar signs (% of patients)	100	40
Electroencephalographic periodic complexes (% of patients)	0	94
Pathological changes	Diffuse amyloid plaques	Sparse plaques in 10%

*Data on the new-variant disease are from Will et al.[74] and Zeidler et al.[75,76]

NEUROPATHOLOGIC CHARACTERISTICS of vCJD

- Significant amyloid plaques surrounded by vacuoles (florid plaques)
- Spongiform changes sparsely distributed throughout the cerebral cortex

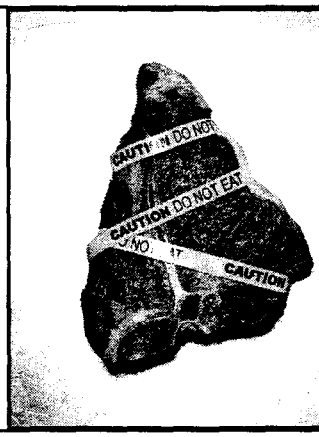


Monitoring for CJD/vCJD

- Suspect CJD cases to be autopsied
- Monitor death certificates for CJD
- Submit specimens to Prion Disease Pathology Surveillance Center at Case Western Reserve University

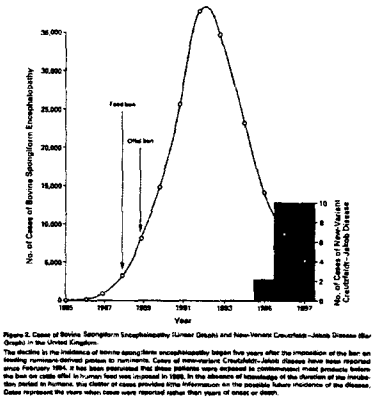
DIAGNOSIS

- Only by post-mortem techniques
- 2 proposed anti-mortem techniques include
  - Detection of the 14.3.3 brain protein marker in CSF
  - Detection of prion protein from tonsil of individuals with NV-CJD



THE LINK BETWEEN BSE AND vCJD

- **Temporal / geographic association**
- **Macaque monkeys infected with brain from BSE-infected cow developed symptoms and pathological changes similar to vCJD**
- **Laboratory studies ("strain typing") show identical distinct molecular features (which differ from sporadic CJD)**



From Bovines to Humans

- **Mechanically removed meat from the spinal cord which were permitted in most cooked meat products (i.e. hot dogs, sausages, meat pies, tinned meats, etc.)**
- **Less Likely:**
  - Contamination of muscle (meat) with nerve tissue emboli from humane stunning
  - Cross contamination of slaughterhouse tools

Leicestershire Study, UK 2001

- **Five individuals with vCJD lived within 5 kilometers of each other**
- **Age of Onset = 22 years (range 17 – 34)**
- **Deaths occurred between Summer '98 and Fall '00**
- **Study showed an association between vCJD patients and consumption of beef from a butcher where there was a risk of x-contamination with bovine brain.**

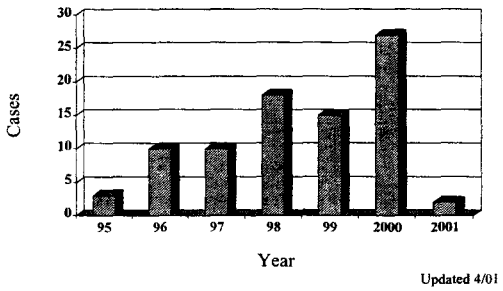
Prion Infectivity of Different Tissue/Organ Types

Category	Infectivity	Tissue/Organ
1	High	Brain, spinal cord, eye
2	Median	Ileum, lymph nodes, spleen, tonsil, dura mater, placenta, CSF, pituitary gland, adrenal gland
3	Low	Distal colon, peripheral nerves, bone marrow, liver, lung, pancreas, thymus
4	Not detectable	Blood, feces, heart, kidney, milk, ovary, serum, muscle, bone, skin, urine, etc.

UK BSE/vCJD EPIDEMIC

- **177,780 bovine cases on 35,156 farms** (3/02/01)
- **97 definite and probable vCJD (Human) Cases** (3/30/01)

vCJD Cases
United Kingdom, 1995-2001



Updated 4/01

CONTROL OF BSE AND vCJD

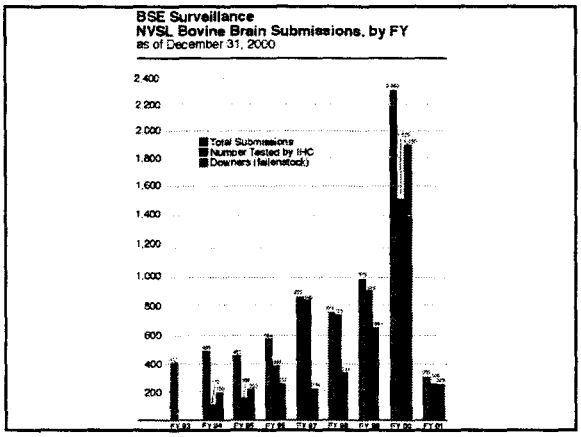
- All suspect cattle are killed, sent for diagnosis, then incinerated
- European Union requires destruction of the entire herd if BSE identified
- To prevent transmission into animals or humans, the head, spinal cord, spleen, tonsils, intestines and thymus are removed and incinerated

Prevention and Surveillance
United States

- Import regulations
- Surveillance
- Risk Assessment
- TSE Working Group

Actions to Prevent Bovine Spongiform Encephalopathy

- Ban importation of live ruminants and most ruminant products (1989)
- Outreach and education to veterinarians, producers, and laboratory diagnosticians
- Active surveillance of "downer cows" (1993)
- Strengthen the Scrapie Control program



FDA REGULATIONS

- In 1997, the FDA established regulations that prohibit the feeding of most mammalian use of proteins to ruminants.

Risk of CJD from Blood

- No epidemiological evidence
- Limited experimental evidence
- Products from patients subsequently diagnosed with CJD are withdrawn

FDA Blood Donor Deferral Criteria, January 18, 2001

- Donors with or at risk for CJD (sporadic, familial, or iatrogenic) or vCJD
- Lived in U.K. for cumulative total of 6 months between 1980-1996
- Lived in France, Ireland, Portugal for cumulative total of 10 years or longer, 1980-present

CWD Precautions for Hunters

- Don't eat ill animal
- Wear rubber gloves when dressing carcass and avoid contact with brain and spinal tissue
- Don't eat brain, spinal cord, eyes, spleen, lymph nodes

Predictions of vCJD

- If the incubation period is 20 to 30 years = upper limit of 3000 cases
- If the incubation period is < 20 = upper limit of 600 cases

Questions?

- Has BSE or vCJD been documented in the U.S.?
- What type of TSE has been documented in MN?
- Do all TSE's behave the same?