



Bovine Spongiform Encephalopathy (BSE): Anatomy of an epidemic

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Objectives

- Review the BSE epidemic
- Investigate factors contributing to BSE emergence
- Discuss the appearance of new variant Creutzfeldt-Jakob Disease
- Highlight risk analysis approaches to “managing” BSE

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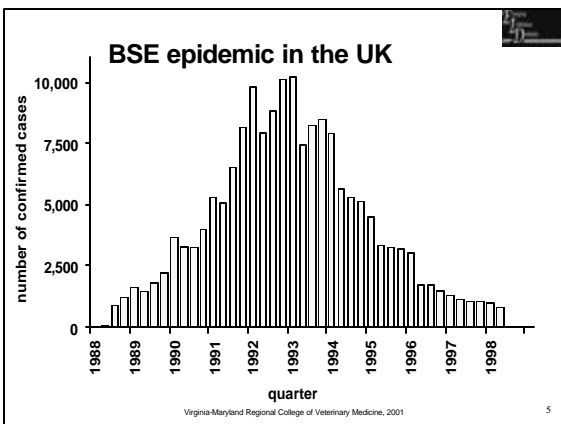
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The BSE epidemic

- First identified in 1986
- Neurologic disease of cattle - increased anxiety, startle easier, incoordination
- Rapid spread throughout UK
- No historical evidence of the disease

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Current BSE statistics for UK

- 176,809 cases thru June 2, 2000
- >4,325,000 cattle destroyed

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BSE Basics

- Common source, extended epidemic
- Feedborne, associated with contaminated meat and bone meal
- Long latency period, 4-5 years
- Classified as a transmissible spongiform encephalopathy

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Transmissible Spongiform Encephalopathies (TSE's)

- Bovine Spongiform Encephalopathy (BSE)
- Scrapie-Sheep and Goats
- Transmissible Mink Encephalopathy (TME)
- Chronic Wasting Disease (CWD)-mule deer and elk
- Kuru
- Creutzfeldt-Jakob Disease (CJD)
- (spontaneous, iatrogenic, familial)
- Gerstmann-Straussler Schenker Syndrome (GSS)
- Fatal Familial Insomnia (FFI)

} Humans

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Similarities of all TSEs

- Unconventional, infectious agent
- Progressive degeneration of the brain
- Neurological signs, always fatal
- No treatment
- No immunological response
- Infectivity difficult to inactivate

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Transmission of TSEs vary

- Oral transmission - Kuru, TME, BSE, scrapie
- Maternal transmission - scrapie, BSE
- Iatrogenic - CJD, scrapie
- Genetic predisposition - scrapie, CJD, GSS
- Spontaneous - CJD, others?

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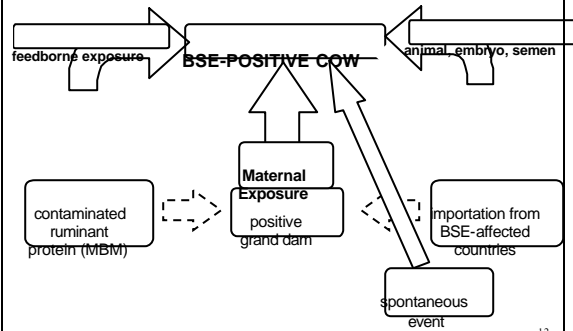
Unique attributes of BSE

- Primary means of spread - contaminated animal feed
- No genetic risk factors to date
- Limited tissue distribution of infectivity detected to date
- Not host specific

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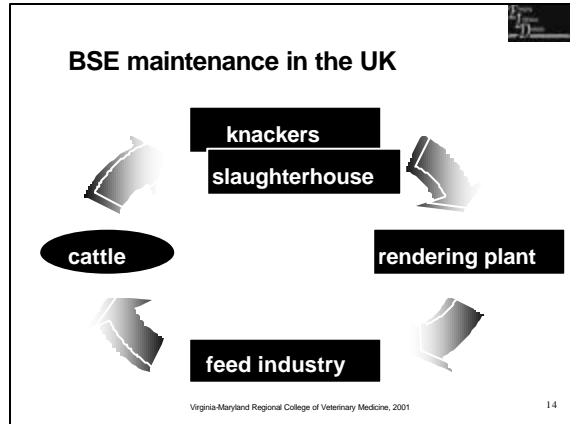
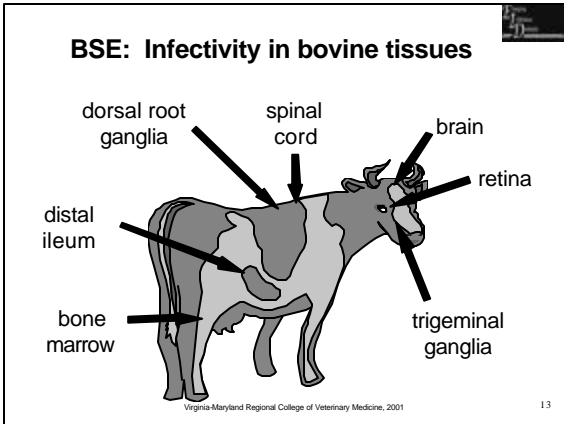
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Potential Events Leading to a BSE-Positive Cow



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BSE emergence in the UK: Two hypotheses

Sporadic cattle disease or **Scrapie**

- High sheep density and scrapie incidence
- Changes in rendering process
- Feeding of animal-derived protein

➔ Emergence of a new TSE strain

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The 'sporadic' or 'spontaneous' BSE hypothesis

- Proposed by Marsh to explain transmissible mink encephalopathy
- TME seen in mink eating 'downer' cows
- 'Spontaneous' BSE not confirmed to date
- Hypothesized to occur at 1/1,000,000 similar to spontaneous CJD

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Expansion of the BSE epidemic

Movement outside of the UK

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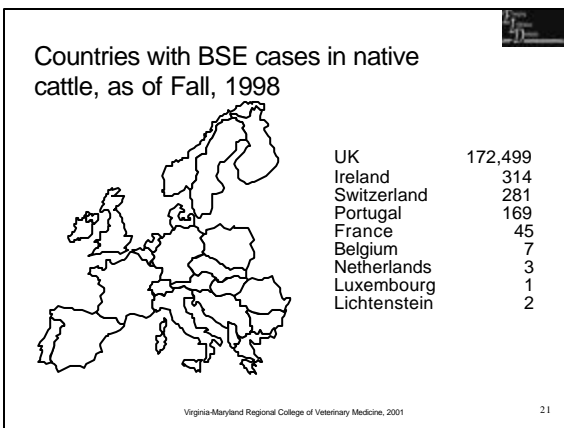
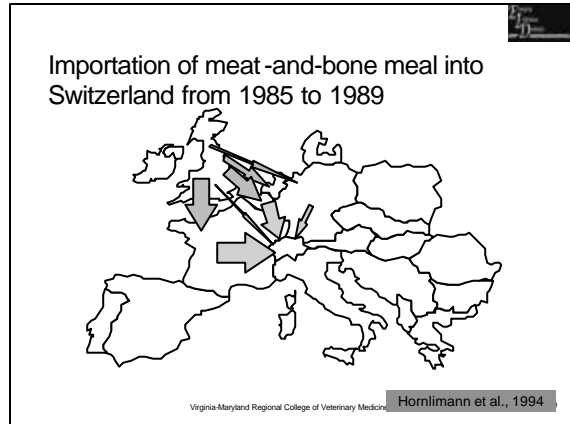
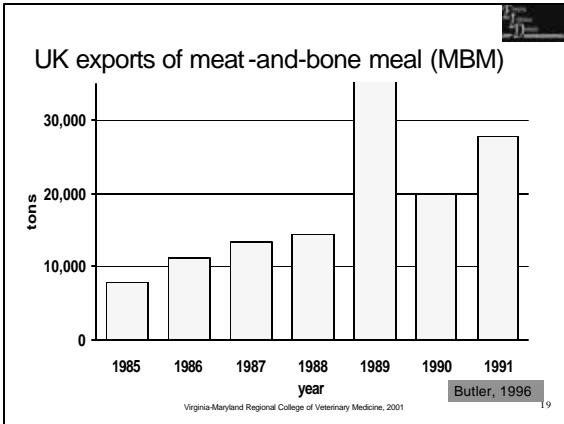
Potential BSE cases imported into some EU countries, 1985-1989

	Imported Cattle	Expected Beef	Expected Dairy	Reported Cases*
Germany	6,343	30	334	6
Spain	2,769	6	74	0
Italy	1,421	6	68	2
Netherlands	1,434	5	62	0
Denmark	889	3	40	1
Benelux	572	2	24	0

* Cases occurring in imported cattle only

Schreuder et al., 1997

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- ### BSE Control
- Identification and destruction of BSE affected cattle
 - Import restrictions from BSE affected countries (cattle and feed)
 - Feed bans - removing ruminant-derived animal protein from ruminant feeds
 - Destruction of exposed animals
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- ### Unresolved BSE issues
- What is the pathogenesis of BSE?
 - Does BSE infectivity exist in further tissues?
 - How large is the cattle to mouse species barrier?
 - Has BSE transmitted to Sheep?
 - If so, will it be maintained by sheep?
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Recognition of BSE as a Zoonotic Disease

The appearance of new variant

Creutzfeldt-Jakob Disease in humans - 1995

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New variant of Creutzfeldt-Jakob Disease

New variant differs from Classic CJD

- Average age 26 yrs compared to 65
- Presenting signs psychiatric rather than neurologic
- Clinical course longer (>12 months)
- Neuropathology different

Evidence that new variant CJD is human BSE - #1

Place and time Will et al., 1996

- New human TSE observed in UK and not seen in other countries*
- Emergence of new human TSE follows discovery of BSE 10 years earlier

* only 1 case seen outside UK to date

Evidence that new variant CJD is human BSE - # 2

Molecular analysis Collinge et al., 1996

- Glycoform analysis creates molecular "fingerprint"
- Unique pattern for nvCJD (type 4), different from other forms CJD
- nvCJD pattern similar to that of mice and others inoculated with BSE

Evidence that new variant CJD is human BSE - # 3

Bioassay in mice Bruce et al., 1997

- Inoculation of 4 inbred mice strains creates biological "fingerprint" of incubation times and lesion profile
- Bioassay of nvCJD different from other forms of CJD and scrapie
- Bioassay of nvCJD same as BSE and others inoculated with BSE

Potential sources of human exposure to BSE

- Direct contact to affected cattle - no cases in exposed humans to date
- Contact with specific products containing infected materials - no common exposure to date
- Consumption of food contaminated with infective cattle tissues - numerous candidates

Meat product concerns for BSE contamination

- Rib roasts, T-bone ➤ dorsal root ganglion (DRG)
- Bone-in meat ➤ bone marrow
- Mechanically-recovered meat ➤ spinal cord, DRG
- Head meat ➤ brain leak, trigeminal ganglia
- Sausage casing ➤ distal ileum
- Ground meats ➤ brain, spinal cord

CJD Statistics from UK (through Sept 30, 1998)

Unresolved nvCJD issues

- How many cases will occur?
- What is the cattle to human species barrier for BSE?
- What is the pathogenesis of nvCJD?
- Is the tissue distribution of infectivity the same for nvCJD as for CJD?
- Can nvCJD be transmitted iatrogenically?

Cattle derived products are ubiquitous in pharmaceuticals

- Tallow - the cooked fat derived from the 'rendering' of animal waste
- Gelatin - produced from animal hides and bones
- Blood, serum, tissue infusions - for bacterial and viral culture media
- Calcium stearate, bone charcoal, collagen - for a variety of products

Exclusion of TSE agents is challenging

- No immune response of the host
- Live animal screening tests are not available
- Surveillance programs in countries vary widely
- Hypothesis of 'spontaneous' BSE haunts some...

BSE (and all TSEs) are difficult to inactivate

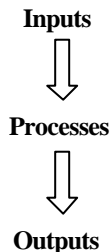
- TSE agents are highly resistant to heat, UV light, ionizing radiation and common disinfectants
- Inactivated by sodium hypochlorite, sodium hydroxide, very high temperatures which denature proteins

End product use questions...

- Can BSE be transmitted to humans through animal-derived products?
- What is the minimum infectious dose of BSE (and nvCJD)?
- To what degree does route of administration affect transmission?
- Is there an 'acceptable' risk?

Applying risk analysis to BSE: a systems approach

- Inputs = raw materials
- Processes = harvesting and manufacturing
- Outputs = end products



The underlying principles of risk analysis:

- Every raw material, process and use involves risks: risks of infectivity, contamination, exposure and illness
- Anything that can go wrong, will go wrong at some point in time
- Therefore, "zero risk" is unachievable

The bright side of risk analysis:

- Multiple safeguards exist to reduce risks to an acceptable level
- Supports decision making in the absence of "perfect" data
- Involvement of the potentially affected parties improves the analysis

TSE risk analysis is different...

- Combines aspects of toxicologic and microbial risk assessments
- In the host, the transformation of PrP^{sc} to the abnormal shape mimics microbial growth
- However, from raw material through the end product, handle like a toxin

TSE hazard identification

- Hazard is BSE
- Not all of the pathways for BSE 'contamination' are clearly understood
- Failure to identify potential pathways will invalidate the risk analysis

Key factors in TSE risk assessment: inputs (sourcing)

- Origin of cattle
 - Country BSE status
 - Herd management
 - Individual animal handling
- Tissue
 - category of infectivity

Confirmed Infectivity of Bovine Tissues

- INFECTIVITY FOUND IN STUDIES OF CLINICAL BSE CASES:
 - Brain, Spinal Cord and Eye (retina)
- INFECTIVITY FOUND IN PATHOGENESIS STUDIES (doses much higher than with infectivity studies):
 - Brain, Spinal Cord, Eye (retina), Trigeminal Ganglia, Dorsal Root Ganglia, Distal Ileum and Bone Marrow

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WHO Categories of Infectivity in Bovine Tissues and Body Fluid

- CATEGORY I: High Infectivity
 - Brain, Spinal Cord and (Eye)*
- CATEGORY II: Medium Infectivity
 - Spleen, Tonsil, Lymph Nodes, Ileum, Proximal Colon, Cerebrospinal Fluid, Pituitary Gland, Adrenal Gland, (Dura Mater, Pineal Gland, Placenta, Distal Colon)

*Tissues in () were not titrated in the original studies, but relative infectivity is indicated by other data on spongiform encephalopathies.

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WHO Categories of Infectivity in Bovine Tissues and Body Fluid

- CATEGORY III: Low Infectivity
 - Peripheral Nerves, Nasal Mucosa, Thymus, Bone Marrow, Liver, Lung, Pancreas
- CATEGORY IV: No Detectable Infectivity
 - Skeletal muscle, Heart, Mammary Gland, Milk, Blood Clot, Serum, Feces, Kidney, Thyroid, Salivary Gland, Saliva, Ovary, Uterus, Testis, Seminal Testis, Fetal Tissue, (Colostrum, Bile, Bone, Cartilaginous Tissue, Connective Tissue, Hair, Skin, Urine)

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Key factors in TSE risk assessment: Processing

- Tissue harvesting is a critical process - contamination concern
- Manufacturing may incorporate TSE partitioning, inactivation, dilution
- Validation of the process is a critical component

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Key factors in TSE risk assessment: End product use

- Exposure dose - how much TSE agent per dose
- Age of patient at treatment
- Number of doses to be expected
- Duration of exposure - length of treatment
- Route of exposure - ic, iv, ip, po, etc

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Ideal TSE risk assessment

- Know the amount of TSE infectivity in the raw materials
- Know the degree to which the infectivity is inactivated
- Know how much infectivity is incorporated into each dose
- Know the use pattern of the product
- Know the susceptibility of humans

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Conclusions

- BSE represents a new cattle disease, widely disseminated but coming under control
- Mounting evidence that BSE causes new variant CJD
- Numerous sources of potential human exposure to both BSE and nvCJD

Conclusions

- Risk analysis provides a tool to manage BSE and nvCJD risk
- Risk analysis is a systematic consideration of raw materials sourcing, process and end product use
- Acceptable risk ultimately will be decided by the consumer...

Questions or comments?

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