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BSE IN SHEEP: SCIENTIFIC FACTS AND UNCERTAINTIES

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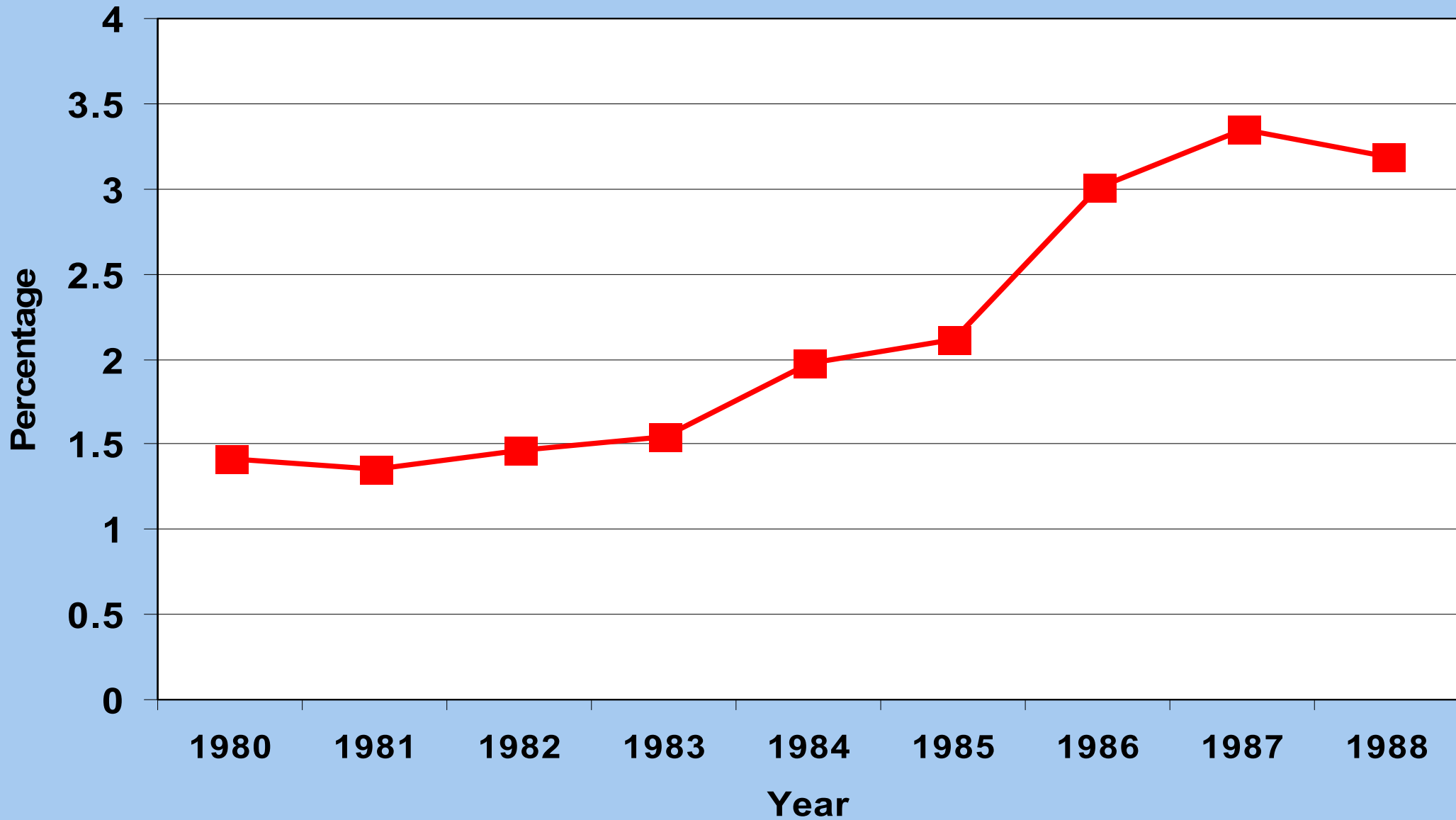
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**Chair, Spongiform Encephalopathy
Advisory Committee (SEAC)**

BSE IN SHEEP: SCIENTIFIC FACTS AND UNCERTAINTIES

- Review the plausibility that BSE entered the sheep flock in the 1980s and 1990s
- Look at the reporting of cases of scrapie – a disease of sheep that presents with similar symptoms and signs
- Summarise the current surveillance for BSE in sheep and discuss problems associated with the interpretation of surveillance data.
- Review the way in which infection with the BSE agent is likely to accumulate in different tissues in sheep
- Summarise the precautionary measures that have been taken in the UK
- Summarise some recent work suggesting what impact additional measures might have in reducing the theoretical risk if SRM controls were extended to further tissues
- Brief overview of the National Scrapie Plan – a long-term strategy to eliminate TSEs in sheep
- List some of the outstanding research questions

MBM fed to sheep as percent of that fed to cattle



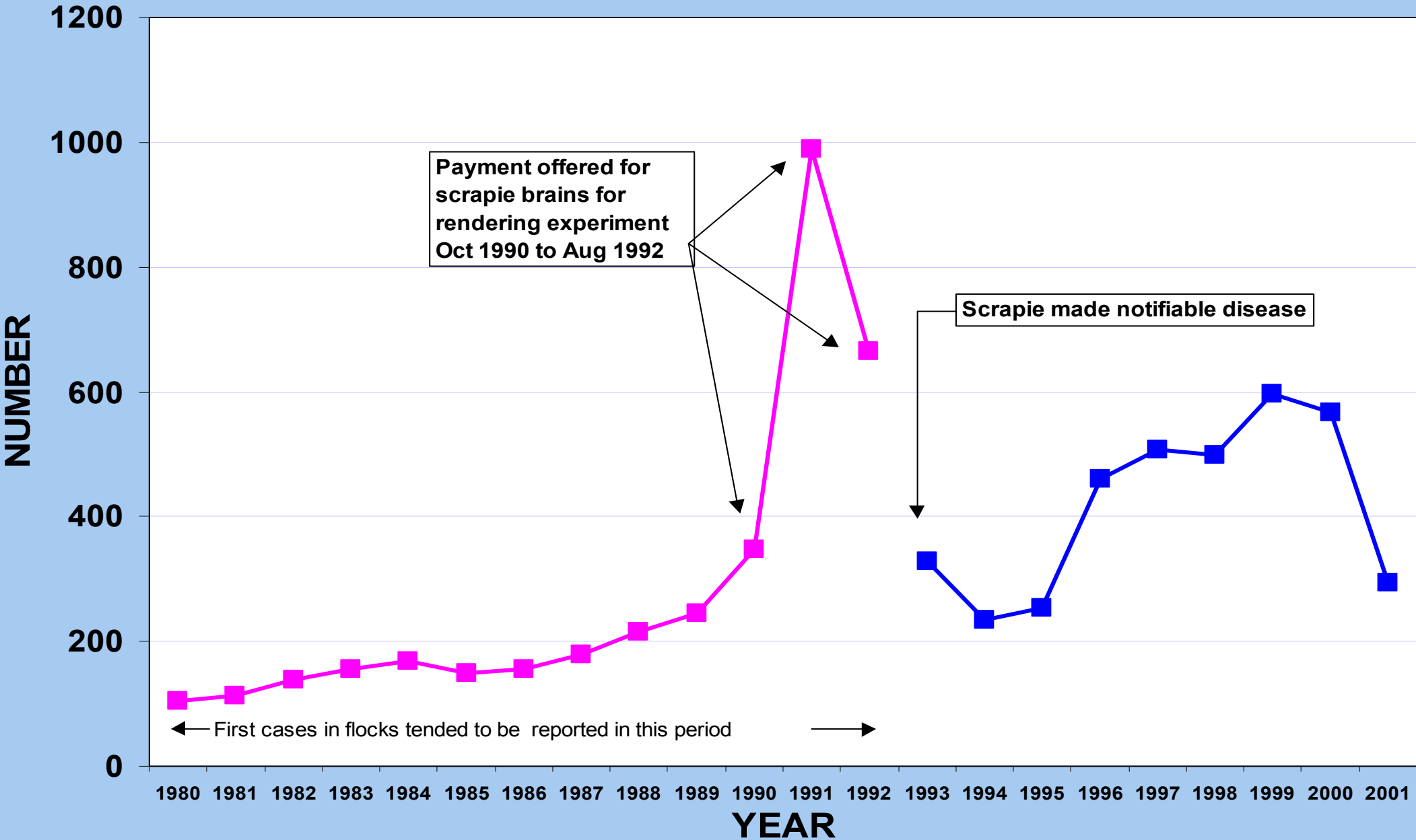
Susceptibility of sheep to oral challenge with 5g BSE brain

Breed	Number succumbed (challenged)	Genotype	Incubation Period
NPU Cheviot	4/5 - 1 healthy at 1631d	AHQ/AHQ	550-935 days
NPU Cheviot	3/5 - 2 healthy at 1333d	ARQ/ARQ	596-1073 days
Romney	4/4	ARQ/ARQ	600 –1130 days
NZ Suffolk	2/4 - 2 healthy at 600d	ARQ/ARQ	~ 600 days
Romney	4/4	ARQ/ARQ	600 –1130 days
Romney	0/12 – 12 healthy at 1000d	ARQ/ARR	
Romney	0/12 – 12 healthy at 1000d	ARR/ARR	

Susceptibility of sheep to oral challenge with 0.5g BSE brain

PrP Genotype	Days after inoculation to TSE	Days after inoculation not TSE
AHQ/ARQ	734	
VRQ/ARR	1945	
AHQ/ARR		756
ARQ/ARR		2155
ARQ/ARQ		2350
ARQ/ARQ		2364
VRQ/ARR		2970
ARQ/ARR		3191
ARQ/ARR		3191

REPORTED CASES OF SCRAPIE IN GB



Postal survey of scrapie in Britain

Hoinville et al (2000), Gravenor et al (2000)

- Postal survey of scrapie incidence among 11,554 sheep farms
- 61% response rate - 15% of respondents reported ever having a case of scrapie and 2.7% had a suspect case in last 12 months
- data suggest that only about 13% of farmers with suspect cases of scrapie are reporting them
- tried to reconstruct scrapie incidence 1962 to 1998
- data indicated gradual linear increase in scrapie over past 36 years
- no evidence of substantial increase during the cattle BSE epidemic
- data cannot be used to determine whether any sheep infected with BSE but they do suggest no large epidemic during 1980s and 1990s

POSSIBLE EXTENT OF FEED-INDUCED CASES OF BSE

- Kao et al (2001) used mathematical modelling to examine a number of scenarios based on the dose response of sheep to BSE, levels of exposure to contaminated feed and numbers of BSE susceptible sheep
- In the most pessimistic scenario presented there were under 10,000 sheep infected with BSE during the period 1986 to 1995 and about 600 cases of clinical disease in the same period
- In their optimistic scenario the number of cases is near zero and there are less than 100 infections
- If there were several hundred cases of scrapie that were in fact due to the BSE agent in this period this would probably not have been detected against the background level of scrapie
- Assuming there was BSE transmitted to sheep by feed, they predict less than 20 clinical cases in 2001 - but stress uncertainties. If present, there is the potential for number of cases to increase with time if horizontal transmission occurs

SURVEILLANCE FOR BSE IN THE CURRENT UK SHEEP FLOCK - MOUSE STRAIN TYPING

- **183 individual scrapie brains inoculated into panels of mice (RIII, C57, VM)**
- **'Indicative' BSE incubation period on primary passage RIII at 320 days, C57 100 days later**
- **176 isolates have been incubating in excess of 320 days in RIII. The status of these are:**

	Positive TSE transmission			No TSE transmission
	RIII only	RIII and either C57 or VM	No RIII, but C57 or VM	RIII, C57 or VM
No. of individual sheep brains	36	45	10	85

SURVEILLANCE FOR BSE AMONG CURRENT CASES OF SCRAPIE - MOUSE STRAIN TYPING

- Failure to find evidence of BSE in 176 scrapie brains tested would enable us to be 95% sure that the percentage of cases of scrapie that are attributable to the BSE agent is less than 1.7%**

Note:

– it will never be possible to prove a “negative”

No tested and all found “negative”	100	500	1000	5000	10000
Upper 95% confidence limit on prevalence	3.0%	0.6%	0.3%	0.06%	0.03%

SURVEILLANCE FOR BSE AMONG CURRENT CASES OF SCRAPIE - MOLECULAR STUDIES

- **Since November 2000, the Veterinary Laboratories Agency have examined material from the brains of suspect cases of scrapie using a Western immunoblotting technique which, although not validated, appears able to show a distinction between BSE and scrapie strains**

Number of scrapie cases examined	Number with BSE-like characteristics
284	0

DIFFICULTIES WITH THE INTERPRETATION OF STRAIN TYPING DATA

- The strain characteristics of BSE may change after passage through sheep - and if BSE is present in the current flock, the infection is likely to have passed through sheep**
- It is important to compare current scrapie cases with experimental BSE that has been passed between sheep (sub-passaged) in a range of genotypes and breeds**
- There are very few 2nd generation cases of experimental BSE in sheep - tissues from BSE-infected sheep have been inoculated into a range of different breeds and genotypes to provide control data for ongoing studies of scrapie**
- One case transmitted by blood transfusion was reported to maintain the BSE characteristics on Western blot**

SURVEYS OF TSEs IN SHEEP

Abattoir survey in 1997/98

(Webb et al, 2001)

- 2809 sheep brains examined (55% under 15 months old)
- No definite positives – 95% confidence limit on prevalence = 0.11%
- Test methods used would not detect early infections – findings compatible with prevalence of infection of 0 to 11%

FROM 2002

Abattoir survey

- 60,000 sheep >18 months (+ve to date = 1/2242)

Fallen stock

- 6,000 sheep (+ve to date = 6/624)

EVIDENCE OF INFECTIVITY PRESENT IN PRE-CLINICAL SCRAPIE IN SHEEP OF MOST SUSCEPTIBLE GENOTYPES

	Period when evidence of infectivity (months)		
	0 - 6	6 - 12	12 +
Brain	-	+	+
Spinal cord	-	+	+
Spleen	+	+	+
Tonsils	+	+	+
Intestines	+	+	+
Lymph nodes	+	+	+

Shaded area indicates presently classified as SRM

RISK ASSESSMENT BY DNV - ASSUMED DEVELOPMENT OF INFECTIVITY

	Relative infectivity by age			
	Lambs <6 mo	Lambs 6-12mo	Hoggets 1-2 yrs	Cull ewes
Brain & spinal cord	0.01%	.1%	10%	100%
Lymph nodes, spleen & tonsil	1%	10%	50%	100%
Intestine	1%	50%	50%	100%
Stomach, liver & thymus	1%	10%	50%	100%
Heart & kidney	1%	10%	50%	100%

RISK ASSESSMENT BY DNV - CONTRIBUTION TO TOTAL REMAINING INFECTIVITY

	Lambs <6 mo	Lambs 6-12mo	Hogget s1-2 yrs	Cull ewes	TOTAL
Brain & spinal cord	0.07%	0.5%			0.5%
Lymph nodes & tonsil	2.2%	18.4%	0.3%	71.8%	83.4%
Intestine	0.1%	4.6%	0.02%	4.5%	9.3%
Stomach, liver & thymus	0.17%	1.1%	0.02%	5.3%	6.7%
Heart & kidney	0%	0.02%	0%	0.1%	0.14%
TOTAL	2.4%	20.0%	0.3%	77.3%	100.0%

NATIONAL SCRAPIE PLAN

- Long term programme to eliminate scrapie
 - breeding programme to increase the genetic resistance of the national flock
 - programme to deal with scrapie infected flocks
 - programme to monitor scrapie with scheme flocks
- Provides scrapie genotyping of breeding rams, electronic ID, and certificates of genotype for each ram, so resistant rams can be used for breeding
- Will use less resistant rams for an agreed period only and cull or castrate the most susceptible ones
- Epidemiological modelling commissioned to re-evaluate a target date for a scrapie resistant national flock

OUTSTANDING RESEARCH QUESTIONS

- **Level of BSE in sheep (if any)**
- **Prevalence of scrapie in sheep**
- **Rapid method for distinguishing BSE from scrapie**
- **Effect of different PrP genotypes on strain characteristics**
- **Change in BSE strain characteristics in sheep-to-sheep transmission**
- **Blood test for TSE infection**
- **Carrier state in sheep genetically resistant to BSE/scrapie?**
- **Levels of infectivity by organ by time since infection in sheep**
- **Mode of transmission of scrapie/BSE in sheep**