

SEAC 24/3

(FOR DISCUSSION AT MEETING 25 - ON MARCH 8, 1996)

**THE RISK TO HUMANS FROM SHEEP.**

The Committee are asked to reconsider the potential human health risks from sheep. This arises from a recent presentation by NPU staff to the Scottish CMO concerning experimental transmission of BSE to sheep, and the subsequent detection of BSE infectivity in the spleen.

Information on the pathogenesis of BSE in cattle is relevant to the discussion, as is the data on transmission experiments using tissues collected from kudu, presented at the meeting of 1 February 1996 (paper 24/2).

The committee may find the appended papers of interest, along with the points of information listed below. They identify occasions when SEAC has previously discussed scrapie and the risk to man, as well as the outcome of experimental exposure of sheep to BSE.

1. Paper 5/6 appended, tabled at the meeting of 19/9/90, discusses the relative risks of transmission of BSE to sheep, and subsequent risk to man. At this stage there was no evidence that BSE could indeed transmit to sheep, or be isolated from non-CNS tissue as a recognisable strain. Paper RB238 by R Bradley (Evidence for changes in the neuropathology of scrapie) was also tabled and discussed.
2. A paper by R M Barlow (Possible changes in the scrapie agent), commissioned following the previous meeting was tabled at the sixth meeting on 1/11/90.
3. The minutes of the twelfth meeting on 28 April 1992, record discussion of the need for a specified offals ban for sheep, particularly in the animal health context, and the possible risks of transmitting scrapie to pigs which could subsequently act as a further reservoir of infection. This discussion arose as a consequence of the report of the Laming Committee. The appropriate paragraphs (8-10) are appended.

Also, at paragraph 17, it is noted that BSE had transmitted to the NPU negative line sheep (Please note that as at January 1996, only one of six challenged sheep was clinically affected after oral challenge, four others have since died, and one remains alive. Following intracerebral challenge, three out of six were clinically affected, two confirmed only on pathology, while one was negative.)

4. Meeting 16, on 26/1/94 - the update on research (16/5) confirmed that BSE had been transmitted to sheep, and that there was clinical evidence of transmission to mice from the spleen of the affected sheep. There would of course have been a delay from the meeting of early 1992 while the bioassay was established.

5. Meeting 17, on 30/8/94 - the research update circulated included further confirmation of transmission from the spleen of the above sheep, still incomplete.

6. Meeting 18, on 10/2/95 - an update from Mr Bradley on the transmission experiments to sheep suggested a confused picture (as indicated by current Research Summary - see table 2 of SEAC 23/1) with variations in clinical picture and pathology.

7. Meeting 19, on 21/6/95 - further update as at paragraph 6.

8. Meeting 20, on 8/9/95 - transmission from spleen of BSE challenged negative line sheep included in Table 6 of new format Research Summary. In the discussion on "research priorities and unanswered questions" at the end of the meeting the committee considered it necessary to know:-

- is there any epidemiological evidence of BSE in sheep;
- if there is evidence for the transmission of BSE from cattle to sheep;
- how does scrapie transmit between animals.

### **Conclusions**

The subject of risk to man from BSE or scrapie via sheep has been discussed previously by SEAC. At that time there was less information available on the pathogenesis of BSE in sheep, but the background data on the potential risk of transmission from cattle to sheep remain unchanged. There have of course been some recent attempts at strain typing "field strains" of scrapie, including some considered to have been of potential food borne origin, and no BSE-like strain has been found.

With the exception of the appended papers the minutes of previous meetings are not detailed enough to aid further discussions or to warrant re-circulation.

D Matthews

## SCRAPIE AND HUMAN HEALTH

Introduction

1. This note considers the possibility that changes may have occurred in the agent causing scrapie in sheep, and the implications for human health if they have.

The evidence for a change

2. Scrapie has been recorded in sheep and goats in the UK and elsewhere for centuries. Considerable research in different parts of the world has shown no causal association between scrapie and similar diseases in man.
3. There is very strong evidence that BSE is caused by the same infectious agent which causes scrapie in sheep. The epidemiological evidence is consistent with two possibilities as regards the agent that causes the disease:-
  - (i) that cattle have succumbed to clinical disease simply because they have been exposed to more of the scrapie agent than they have been in the past; or
  - (ii) that BSE arose from increased exposure to a strain of agent which had previously been selected by cattle and passaged in the species, via meat and bone meal.
4. The epidemiological data do not support the suggestion that cattle might have been exposed to a novel strain of scrapie from sheep. It follows that the continued consumption by man of material derived from scrapie-infected sheep should not alter the view that scrapie has no implications for human health unless BSE is itself a new strain of the agent which has been transferred back to sheep after passage in cattle and is now circulating in the sheep population.

5. Experimental studies have shown that the properties of a single cloned strain of scrapie agent transmitted to another species, may remain unchanged, or may experience a permanent change due to a mutation of the scrapie genome.
6. When scrapie or kindred agents are passaged through a different species a temporary change (the donor species effect) occurs commonly, but not invariably, due not to a change in the scrapie genome but to the fact that the protein associated with infectivity is derived from the donor host. The result is that the length of the incubation period at first passage is reduced and stabilises at subsequent passages, apparently because the protein at second and subsequent passages will be of the same species as the test animal.
7. If mutation had occurred as a consequence of sheep - cattle - sheep passage, the following factors would need to be taken into account in assessing the possibility that the pathogenicity of the agent for man might have altered:-
  - (i) any mutation is as likely to have made the agent less pathogenic as more so;
  - (ii) if a change has occurred, it is not necessarily a recent event. Cattle have been exposed to scrapie-infected sheep material through feed or through contact with infected placenta for many decades.
8. The theoretical possibility that there might have been a change in pathogenicity of the agent as a consequence of recycling infection amongst cattle is the basis of the specified offals ban. This measure, coupled with the slaughter of affected animals, is aimed at reducing human exposure to the agent to levels at which clinical disease would not occur, given an oral exposure route which is very inefficient.

9. There is no evidence that such mutations have occurred in sheep scrapie passaged naturally through cattle. The experimentally induced mutations were achieved with cloned single strains in an in-bred laboratory species following multiple passages. This is quite different from the natural situation where recipients would be naturally heterogeneous.
10. Experimental evidence shows that BSE can be transmitted by bovine tissues, at least brain (the inoculation of other tissues having not yet led to the transmission of clinical disease). Although there is no scientific evidence that sheep are susceptible to BSE by the oral route, the probability is that they would be if exposed to a sufficiently large dose. Sheep appear to be susceptible to scrapie by oral transmission, and as the original cause of BSE was eating scrapie-infected material, it is theoretically possible that a new strain which had emerged as a result of exposure of cattle to the scrapie agent could have been reintroduced into sheep by the consumption of meat and bone meal containing infected material (although this would have required a second crossing of the species barrier). Since July 1988 the feeding of sheep with protein rations derived from ruminant material, including brain (and other tissues known to carry the scrapie agent), has been banned. As the vast majority of sheep (over 75%) are slaughtered in their first year, and most of the rest in their second year, only a small and decreasing number of animals directly exposed to possible infection with either scrapie or BSE by the feed route will be slaughtered for human consumption.
11. The feeding of sheep with concentrates grew during the 1980's but it remains at a very low level; the total tonnage of concentrated sheep feed produced in the UK in 1989 was some 410,000 tonnes compared with 3,670,000 tonnes for cattle and calf feed, although sheep meat production equates to some 40% of that of beef. This has to be seen in the context of a total cattle population of 12 million and a sheep population of 40 million. However, of crucial significance was the fact that

prior to the ruminant feed ban only a very small proportion (perhaps as little as a few hundred tonnes) of meat and bone meal was used in sheep concentrate rations out of a total domestic production of 400,000 tonnes of meat and bone meal annually. Although precise figures are not available, conversations with ADAS sheep experts, renderers and compounders bear this out

12. If animal protein was used in concentrate rations it would have been used mainly to feed breeding ewes in the 6 - 8 week period prior to lambing and perhaps for a short period afterwards. The only use in lambs would have been as finished pellets prior to slaughter. Since the ruminant feed ban has been in place for over 2 years, none being slaughtered now will have been fed such material. If breeding ewes were exposed prior to the feed ban there may well have been insufficient time for incubation to have progressed to the point where agent is present in vulnerable tissues. The average lifespan of a breeding ewe is 5 - 6 years. If animal protein was used it would have been at 1 - 2 % of the total diet.
13. The existence of a new strain of scrapie in sheep might be indicated by changes in the clinical signs, pathology, or numbers and distribution of scrapie cases. Although the numbers of scrapie cases reported to VI centres rose during the 1980's (see Annex), they are still too small to enable any meaningful conclusions to be drawn and are, in any case, thought to be unrepresentative of the actual situation. Investigations are continuing into possible changes in the pattern of scrapie lesions, but so far no significant change has been found. While it is possible that some change might have occurred in scrapie, the available evidence does not support this hypothesis.
14. If BSE is a new strain of scrapie, the route by which it might have been reintroduced into sheep was blocked by the ban on feeding ruminant protein to ruminants. But if it had been

reintroduced before July 1988 and if, like other forms of scrapie, it were naturally transmissible, it is possible that the new infection could be maintained in the sheep flocks alongside other strains. If BSE agent replicated relatively quickly in sheep (as it does in mice) it might become the dominant sheep strain within susceptible appropriate genotypes.

15. Any theoretical hazard to man would exist from the consumption of material from the lymphoreticular and central nervous systems of animals old enough for the agent to have multiplied. Data are not available on the ages at which adult sheep are normally slaughtered, but the ratio of lambs slaughtered to adult sheep is 10:1. Of the animals slaughtered as lambs, about 85% are slaughtered in the calendar year of their birth (i.e. at less than ten months old), and the rest are kept for slaughter in the early months of the following year. The bulk of British live animal exports are believed also to be slaughtered as lambs. Therefore the large majority of British animals are slaughtered before any infection has had time to multiply to high levels. And in any case none being slaughtered now will have been fed on concentrates containing animal protein. The major use for human consumption of sheep lymphoreticular and nervous system material is in the use of lambs' gut for sausage casings. Studies have been carried out on the extent to which such material from cattle would, when used in this way, retain significant amounts of lymphatic tissue, but similar work has not been done in the case of sheep.

Possible action: public health

16. The bovine offal ban has been imposed because of a theoretical possibility that in the transfer from sheep to cattle the scrapie agent might have increased pathogenicity for man. It is not based on any evidence or any quantified risk assessment. There is a similar theoretical possibility, although there is no evidence for it, that if such a new agent exists it might also be present in the sheep population. But there are factors

which make such a situation less likely than the original transfer of BSE to cattle:-

- a further species barrier would have had to be crossed;
  - sheep would have been less exposed to the BSE agent than cattle to scrapie, because of the lower use of compound feed for sheep. (There has been no direct exposure since July 1988);
  - recycling in cattle, except at levels incapable of producing clinical disease, may have occurred for only a short time.
17. If the BSE agent were present in sheep, the risk to human health would be less than any risk arising from BSE in cattle, because the large majority of animals are slaughtered before the agent has time to multiply in the vulnerable organs. If current experimental results were maintained, this would suggest differences in the infectivity of the organs measurably infected with BSE as compared with scrapie could point to the possibility that those sheep organs most used for human consumption would not be infectious.
18. Nevertheless, if it was felt to be a significant risk that a form of scrapie might be hazardous to man, the response to be considered would, on the BSE analogy, be a ban on the use for human consumption of those sheep offals most likely to harbour the BSE agent, or possibly the destruction of infected animals and their milk, which would of course produce huge practical and economical problems.

Control measures: animal health

19. It is widely accepted that in the absence of an effective test for use in the live animals, and an identification system for sheep on a national scale, there are massive obstacles to a scrapie eradication programme. Simply making scrapie



compulsorily notifiable would be extremely expensive because the disease is widespread and also because of the need to resort to confirmation by detailed histological examination in the laboratory. There would need to be a clear objective in view if the very large resources required for such action were to be justified.

### Research

20. Some of the research work currently under way is directly relevant to the question of whether the scrapie agent has changed in cattle, namely:-

- strain typing of isolates from sheep and comparison with strain types of BSE in natural cases;
- some of the Research Council-funded work at IAH on the fundamental aspects of slow viruses;
- aspects of the pathological and epidemiological work being undertaken at CVL;
- work at CVL and IAH on the detection of BSE at the subclinical stage.

### Conclusion

21. For about 4 years, some sheep were likely to have been fed material derived not only from scrapie-infected sheep but also from cattle infected with BSE. In theory, ovine BSE could have altered pathogenicity compared with scrapie for sheep and other species, possibly even man. It is clearly right for research work on BSE to have in mind the possibility that this might have occurred, although as yet there appears to be no evidence for this either way.

22. The Committee is invited to review the evidence available and to advise on any possible implications for human or animal health, and on any necessary changes to the current research programme.

SHEEP POPULATION IN THE UK

Breeding flock total	=	21 million
of which		
Ewes	=	20.5 million
Rams	=	.5 million
Lambs under 1 year	=	22 million
TOTAL	=	over 43 million

Sheep scrapie in Great Britain

Scrapie is not a notifiable disease. However, the returns for the diagnostic work carried out at the Ministry's Veterinary Investigation Centres and the Scottish Colleges show the following number of incidents:-

1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
94	100	129	143	153	143	153	176	211	224

An accurate assessment of the true incidence of scrapie in the national flock is not possible to make.

RB238

has file: the Tynell case has  
 was dealt for the long with  
 the possible change in scrapie agent  
 Hadlow

IN CONFIDENCE

A STUDY AIMED AT DETERMINING WHETHER OR NOT THERE HAVE BEEN  
 SIGNIFICANT CHANGES IN THE NEUROPATHOLOGY OF SCRAPIE IN SHEEP  
 AND GOATS DURING THE LAST TWO DECADES IN MATERIAL SUBMITTED TO  
 CVL PATHOLOGY DEPARTMENT

INTRODUCTION

Only a proportion of scrapie cases reported in VIDA are submitted to Pathology Department by the VIS. This study is so far incompletely reported and is presented in confidence especially as it includes comparison with research results from NPU which are not yet published. The study was conducted by Mr J Wood under the guidance of Dr S H Done and Dr W J Hadlow.

MATERIAL AND METHODS

All scrapie positive submissions to CVL Weybridge since the early 1970s (250 since 1984) have been re-examined with a view to classifying them broadly by the type and distribution of lesions and attempting to demonstrate correlation with any other submitted data (eg breed, age, feeding practice, geographical distribution). This data is however incomplete. Unexpected or unusual findings were discussed with Dr W J Hadlow and Professor R M Barlow. The neuropathology of these cases was compared with that induced experimentally by i/c inoculation of BSE agent into sheep and goats at NPU (by courtesy of Dr H Fraser).

RESULTSSheep

The range of lesion type in natural sheep scrapie varies from that described in the classical texts. In particular the cerebral cortex (neocortex) is not uncommonly affected, sometimes severely.

The nature and distribution of lesions can be generally classified into a small number of groups which commonly but not exclusively correlate with breed. This suggests that there may be particular agent strains which are associated with certain breeds or a genetic variation in sheep that is correlated with breed.

The cortical lesions are not new and have been well recognised in sheep by Professor Barlow. The date of the first case seen with cortical lesions was 1978. However, early cases of scrapie (1970s) rarely had examination of other than the brain stem.

The occurrence of high incidence of scrapie in some flocks seen in recent submissions is nothing new over the period. Many of these can be related to introduction of tups.

The pathology of Cheviots and goats inoculated with BSE is quite different from that of field scrapie. Only one recent sheep submission has a similar pathology.

The conclusion is that there is little evidence for a change in the neuropathology of scrapie in sheep from the 1970s to date. If the singleton case, which is similar to experimental "BSE in sheep", has an origin in a food-borne source then it would appear to be very rare.

#### Goats

Cortical lesions in goats have also been recognised and had not previously been seen by Professor Barlow (who had seen very little natural goat scrapie anyway), or by Dr Hadlow. The significance of this is unclear. There is at present no evidence that cortical lesions are correlated with feeding practices. The number of goat submissions has been much less than those of sheep.



R Bradley  
13 September 1990

Mr R C Lowson (re Tyrrell)  
CVO (for information)  
Dr B J Shreeve (for information)  
Dr T W A Little (for information)

Tabled at Tynnell die on  
1 Nov.

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Mr K. Taylor

② Mr Lawrence + per 

POSSIBLE CHANGES IN THE SCRAPIE AGENT

R M Barlow

Mr Marki

If as is believed the epidemic of BSE is a consequence of concentrate feedstuff-borne scrapie infection, it is possible that changes in the prevalence and patterns of scrapie may also have occurred through similar concentrates being fed to sheep and goats.

The feeding of concentrates to small ruminants is variable. It is least in hill sheep and fibre-producing goats and greatest in dairy goats, milking sheep and Downs breeds going for early lambs.

Thus the intention was to try to focus on the latter groups and compare the situation a decade ago with the last five years. Information has been sought on prevalence, breed/species distribution and any differences in patterns of pathology especially relating to cerebral cortex and age at onset.

I have concentrated on Scotland; the following information has been obtained from the Moredun Institute whose neuropathological diagnostic service handles material from all 8 Scottish VI Centres and to a variable extent those at Penrith and Newcastle.

Data presently available is "muddy". Computerised records only go back to June 1983; for economic reasons the number of blocks taken from suspect scrapies has been reduced from 11-13 to 4-5 concentrating on brain stem and archival material more than 10 years old has been drastically reduced. Furthermore the Shetland County Council/HIDB sheep health scheme material which includes scrapie has since 1986 been channelled through the Thurso VI Centre without being identified separately from mainland cases.

I am indebted to J S Gilmour FRCVS at Moredun for the following information:

	<u>Confirmed Scrapie Cases Total</u>	<u>(% age of total submission) excluding Thurso</u>
1983 (June et seq)	6 (0.9%)	5 (0.8%)
1984	24 (1.8%)	22 (1.7%)
1985	25 (2.2%)	20 (1.7%)
1986	32 (2.5%)	22 (1.7%)
1987	27 (1.9%)	12 (0.9%)
1988	38 (2.7%)	17 (1.2%)
1989	46 (4.4%)	24 (2.3%)

No real pattern here but a trend could emerge with the 1990 figures.

#### Archival material

Slides/blocks are available as follows :-

1977	3 cases
1983	6 cases
1984	24 cases
1985	17 cases
1986	32 cases
1987	21 cases

The material from 85 - 87 may not be comprehensive. Currently, at my request full sets of blocks are processed to paraffin but may not be cut routinely.

Between 1979 and 1984 Anne Mackellar (Moredun) and I produced lesion distribution diagrams of naturally occurring and experimental scrapie cases with the intention of assessing any breed, regional or agent strain correlations. We had at least 7 groups within which there were subgroups and quite a lot of overlap. My recollections of this work are that cortical lesions in sheep were mild and none other than in the New Milton Suffolk flock which bred itself to extinction.

Since I have been at RVC I have examined rather fewer cases than formerly and rather more in goats than in sheep. I have been struck by the prevalence and severity of cortical lesions (mainly in the prefrontal and parietal regions) in many cases. However James Wood (CVL) has just completed an examination of goat material going back at least 20 years and

such lesions were present then as now.

This is a bit anecdotal but the data could possibly be firmed up though it would take time and money.

#### Prospective studies

I have discussed some possibilities with a pedigree sheep breeder who is also a veterinarian. He considered that many of the bigger breeders "have gone into their shells" since the advent of BSE and have a considerable moral dilemma - increased trade with Eastern Europe is now possible but requires owner declaration of freedom from scrapie.

This moral dilemma is more serious than the financial one of submitting to examination. However, he felt that with guarantees of confidentiality, the waiving of veterinary fees and £20.30 for each sheep "Seized" one might get owner collaboration. Owners of small flocks (<100 sheep) and minority breeds eg Charollais and Bleu De Maine might be more co-operative than Suffolks/Dorsets etc. He also felt that co-operation was more likely from S.W. England than Scotland! The Suffolk Health Scheme started by the late M.B. Parry, if still extant, might be a good place to start (convenor Bill Steel).

The National Sheep Association is clearly worried and has called together 6 people from the veterinary and production sides of the industry to discuss matters - hence my apologies for absence today. I will report on the meeting to Dr Tyrrell.

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Handwritten notes: "The Committee were content with the Laming Group's emerging views as to the difficulties surrounding a relaxation of the ruminant feed ban even once the requirements for neutralisation were clear. This would not however justify abandoning the experimental work, as it was important to know what mechanisms were operating."

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Handwritten notes: "The Committee had some sympathy for the Laming Group's view that further work needed to be done on the susceptibility of pigs to SE's. But given the likely level of incidence of disease it was not likely that results from exposing say twenty pigs would be much more value than those arising from exposing ten. The questions to which an answer was ultimately required were:"

8. The Committee had some sympathy for the Laming Group's view that further work needed to be done on the susceptibility of pigs to SE's. But given the likely level of incidence of disease it was not likely that results from exposing say twenty pigs would be much more value than those arising from exposing ten. The questions to which an answer was ultimately required were:

- what further could be found about the behaviour of BSE in pigs - in particular, could the agent be passed to the human population without producing clinical signs in pigs;
- was there a risk that scrapie (or BSE recycled through sheep) might affect pigs and provoke another epidemic like BSE in cattle.

Possible approaches included examining the PrP gene in pigs to assess its uniformity as between individual animals and its similarity to those in other species; and the use of transgenic mice. Mr Bradley and Professor Barlow agreed to produce a paper to be considered by a future meeting of the Committee.

Handwritten notes: "As regards the advisability of removing from the food chain the heads of sheep suffering from scrapie, they noted that the quantity of lymphoreticular and nervous tissue in a sheep carcase exceeded that of brain tissue; so simply to remove brains from the food chain would not have much effect on any problem that might exist. If a case for action could be established, then the implication was that there would need to be an extension of the specified offals ban to sheep. But this would have enormous practical implications and there was no epidemiological or other evidence that there was a"

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problem. The Committee therefore concluded that the presence in animal feed of sheep brains, nervous tissue and lymphoreticular tissue did not represent a high risk. If any action were called for, then the first step would be to improve surveillance mechanisms, if the Laming Group felt that these were not adequate.

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However the Committee agreed that one possibility that should be examined was that as a result of the recycling of BSE through sheep, potentially dangerous changes in the scrapie agent might have occurred. Epidemiological study was likely to be a key element in this, supported by laboratory studies of the behaviour of the scrapie agent in mice. Mr Wilesmith might be asked to consider what new work should be done on scrapie.

11. On tallow, the Committee's view that further restrictions were not needed had been based on assurances from MAFF that tallow derived from SBO's did not get into the food chain. The Laming Group would need to satisfy itself that this was the case. It might be appropriate for MAFF to explore the issue further.

12. Professor Laming had, after the meeting, asked the Committee to consider some further questions:

(i) What is the Committee's view of the infectivity of tissues in animals infected with scrapie before clinical signs emerge?

The data on this were well documented. The presence of detectable infectivity in tissues was summarised in a note which Dr Kimberlin did as part of a paper prepared for discussion in OIE, which the Secretariat agreed to forward to the Laming Group.

SEHC MINUTES 2814192

## I. RESEARCH UPDATE (SEAC 12/3 AND RBSB.4)

16. The Committee took note of the report of the CVL/NPU meeting. Reports of SE's in captive puma and cheetah further weakened the Southwood Working Party's view of the likely limited host range of SE's. Mr Bradley reported that it had been decided to terminate the mouse transmission experiments at 700 days after inoculation, and to sub-passage material from mice inoculated with the spleen of BSE cases.

17 The Committee were grateful for the detailed progress reports on transmission experiments. The agent of BSE, and of newly reported SE's in other species, appeared to be behaving differently from scrapie; disease had been transmitted to negative-line cheviot sheep, and there appeared to be no variation in behaviour as between species of origin in disease transmitted to mice from kudu and nyala. It was also noted that TME appeared to have induced disease in mice after passage through cattle, although it did not do so by direct inoculation. Finally, the Committee noted that intra-cerebral and intra-peritoneal inoculation gave different results, which suggested that intra-peritoneal inoculation was not necessary in transmission experiments.

## J. SE's IN CATS (SEAC 12/4)

18. The key reasons for studying the disease in cats were to determine the extent of the disease and to understand why some animals succumbed and some did not. The latter aspect had been the purpose of the study which AFRC had initially proposed to support but which had been aborted<sup>partly</sup> as a result of MAFF's refusal to provide BSE material for inoculation into cats. The Committee asked MAFF to reconsider this issue.