DEPARTMENT OF HEALTH
MINISTRY OF AGRICULTURE, FISHERIES & FOOD

REPORT OF THE WORKING PARTY
ON BOVINE SPONGIFORM ENCEPHALOPATHY

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February 1989
To The Secretary for State for Health, &
   The Minister for Agriculture, Fisheries and Food,

As you know, in April 1988 I agreed to chair a Working Party which was to be set up to
examine all aspects of the newly identified cattle disease called Bovine Spongiform
Encephalopathy (BSE) and to advise accordingly.

Following the first meeting of the Working Party on 20 June 1988, I wrote to your
Departments with two recommendations which we considered needed urgent attention. The
first was that as a precautionary measure, at least until more is known about BSE, the
carcases of affected animals should be destroyed. The second was that an expert
Consultative Committee on Research should be established to advise on the research
which is in hand and that which is required to answer questions identified by this
Working Party. I am very pleased that the Government accepted and implemented both
these recommendations, as described in the Report.

Three further recommendations were made following the second meeting on 10 November
1988. These were, firstly, that the ban on the use of ruminant-based protein in
rations for ruminants should continue indefinitely. This recommendation was made
because the Working Party could not be wholly sure that rendering as currently
practised would eliminate the agents causing BSE. In addition, although the
transmission of BSE via milk is very unlikely, we recommended that milk from suspect
BSE cattle should be destroyed as a precautionary measure. Finally, we re-emphasised
a point made in my earlier letter, namely, that it was vital to be able to "keep tabs"
on offspring of affected animals in order that the question about maternal
transmission can be answered.

Again I am pleased to be able to record the Government's positive response with the
prohibition on the use of milk from suspect animals for human or animal consumption
and an extension of the feed ban throughout 1989, together with a statement by the
Minister that it will be necessary to continue the feed prohibition beyond the end of
1989 unless processing methods which are sufficient to destroy the agent have been
identified and are widely available.

We have now had an opportunity to consider further various aspects of this new disease
problem and accordingly make a number of recommendations. However, we wish to
emphasise that in several areas the need for any further action will be dependent on
the results of research into the disease. Furthermore, because of the nature of the
disease, particularly its long incubation period, results cannot be expected for some
time. In the circumstances the recommendations focus on the importance of this
research. We have tried to identify the main areas of research which we regard as
essential and those which should be considered by the newly established Consultative
Committee on Research.
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1. INTRODUCTION

1.1 The establishment of the Working Party on Bovine Spongiform Encephalopathy (BSE)

In May 1988 a Working Party was established to examine the implications of Bovine Spongiform Encephalopathy (BSE), a newly identified neurological disorder of cattle, in relation to both animal health and any possible human health hazards and to advise the Government on any necessary measures.

1.2 Membership

The membership: Professor Sir Richard Southwood, PhD, DSc, F.I.Biol, FRS - Linacre Professor of Zoology, University of Oxford, (Chairman).

Professor M A Epstein, CBE, MD, DSc, PhD, FRCPath, FRCP, FRS - Emeritus Professor of Pathology, University of Bristol.

Dr W B Martin, PhD, DVSM, F.I.Biol, FRSE, MRCVS - formerly Director of the Moredun Research Institute in Edinburgh.

Sir John Walton, TD, MD, DSc, FRCP - Warden of Green College, Oxford; formerly Professor of Neurology, University of Newcastle upon Tyne.

Expert Adviser - Mr J Wilesmith, BVSc, MRCVS - Ministry of Agriculture, Fisheries and Food.

Joint Secretariat - Dr H Pickles, PhD, MRCP - Department of Health.

Mr A J Lawrence - Ministry of Agriculture, Fisheries and Food.

1.3 Terms of Reference

The terms of reference are "To advise on the implications of Bovine Spongiform Encephalopathy and matters relating thereto".

2. HISTORY OF BOVINE SPONGIFORM ENCEPHALOPATHY

2.1 The disease

Bovine Spongiform Encephalopathy (BSE) is a slowly progressive and ultimately fatal neurological disorder of adult cattle. It has been given this name because of the spongy appearance of brain tissue, known technically as grey matter vacuolation, when sections are examined under the microscope. BSE was first identified as an entity by the Ministry of Agriculture, Fisheries and Food's Central Veterinary Laboratory, Weybridge in November 1986 (51), although retrospective consideration of clinical records suggests that it may have occurred as early as April 1985. All the available evidence suggests that BSE belongs to a group of progressive, degenerative diseases of
the central nervous system, which invariably prove fatal. They are caused by a group of unconventional transmissible agents. The other similar diseases include scrapie in sheep and goats, transmissible mink encephalopathy and Creutzfeldt-Jakob Disease (CJD) in humans (43,10,6) [see Section 3].

2.2 Clinical signs

The clinical signs involve behavioural, gait and postural abnormalities and usually begin with evidence of apprehension, anxiety and fear. Some animals may paw the ground or continually lick their nose. There is increased reaction to sound and touch. A swaying gait, sometimes coupled with high stepping of the feet, is most evident in the hind limbs. Signs may progress from reduced milk yield, weakness and loss of condition, to frenzy and aggression. Kicking and general nervousness in the milking parlour are frequently reported signs. The gait abnormalities can be seen on grassland, especially when urged to move at the trot. On concrete, difficulty in turning may be accompanied by slipping and falling. In the advanced stages animals become recumbent (51,48,52).

2.3 Duration of illness and age of affected animals

Following the onset of clinical signs, the condition of the animal deteriorates until it either dies or becomes unmanageable and has to be destroyed. This usually takes anything from 2 weeks to 6 months as illustrated at Figure 1. Since the advent of compulsory notification and slaughter, the average time between notification and slaughter has been 8 days, with over 80% slaughtered within 3 weeks. All the cases of BSE have occurred in adult animals, with an age range of 3 to 11 years. However, most cases have occurred in animals between 3 and 5 years of age as shown in Figure 2. There is evidence that if the animal is stressed, eg on separation from the herd or on being sent to market, the development of clinical signs accelerates (G Wells & J Wilesmith, personal communication).

2.4 Diagnosis

Observations on suspect cases of BSE over a period of time have provided a sound basis for clinical diagnosis. Preliminary studies in relation to the use of electro-encephalograms (EEG) as an ancillary aid to diagnosis have shown that the EEGs in two cases of BSE differed markedly from those seen in similarly aged clinically normal cattle and those recorded from cases of other types of experimental neurological disease in other ruminants (1). The EEG abnormalities also show a striking similarity to those which are usually found in human CJD. Confirmation of disease is however only possible following post-mortem histological examination of brain tissue. The unconventional agent which is thought to cause BSE is quite unlike any bacteria or known viruses. Its structure and manner of replication does not provoke any detectable antibody response in the host. Because of this there is at present no blood or other tissue test available for detecting the disease in the live animal.

2.5 Incidence and distribution of the disease in Great Britain

2.5.1 In the period from November 1986, when the disease was first identified as a separate entity, to 31 December 1988 there were 2160 confirmed cases on 1667 farms. The current incidence is estimated to be in the region of 350-400 confirmed cases a month. This represents an annual incidence of around 1 case per 1000 in adult cattle in Great Britain where the total population of adult cattle is 4 million. As indicated in paragraph [7.2.3] it is considered that this provides an accurate picture
of the incidence of the disease in Great Britain. A feature of the disease so far has been that in the majority of affected herds only a single animal has developed the symptoms (52). Although cases of BSE have occurred in most parts of Great Britain there has been a much higher concentration in the southern half of England. An illustration of the geographical distribution of the incidence and number of dairy herds with confirmed cases up to 31 December 1988 by region and county is shown in Figures 3 and 4.

2.5.2 BSE was made a notifiable disease on 21 June 1988. From that date it became a legal requirement to report suspect cases. Before then most reports of suspect disease were made by private veterinarians to the Ministry of Agriculture, Fisheries and Food's Veterinary Investigation Centres. Up to 21 June 1988 867 cases of disease were confirmed. From then up to 31 December 1988 974 cases were confirmed. The number of cases confirmed by month and year is shown at Figure 5.

2.6 Incidence of disease elsewhere

BSE has not been reported outside the British Isles but two research workers have reported that they suspected the presence of a scrapie-like disease of cattle in the USA (36). However, the combination of critical factors which has probably led to the emergence of the disease in this country [see section 4.2] may not exist in many other countries, if anywhere. These factors include the existence of a sheep population in which scrapie occurs and a feed and cattle industry which produces and uses ruminant-derived meat and bone meal in calf rations.

3. TRANSMISSIBLE Spongiform ENCEPHALOPATHIES

3.1 The causative agents

There are a number of transmissible spongiform encephalopathies affecting animals and man which are caused by unconventional infectious agents (43,6). The agents responsible have not been completely characterised, although their composition appears to be very similar, with a peptide as a major component. There are three conflicting interpretations of existing knowledge (25), the agent being termed either a prion, a virino, or a filamentous virus and defined as follows:

i. "a prion is a small infectious pathogen containing protein (PrP); it is resistant to procedures that modify or hydrolyze nucleic acids." (42).

ii. "a virino is an infectious pathogen containing a core of nontranslated nucleic acid associated with cellular proteins" (30).

iii. a filamentous virus; it being argued that scrapie agent's resistance to inactivation is limited to small subpopulations and is not unlike that of conventional viruses (45).

These small infectious agents have also been termed "slow viruses", "unconventional agents" and "subviral pathogens". They are unusually resistant to heat and to the normal sterilisation processes (31) [see para 3.9 below].
3.2 Animal spongiform encephalopathies

The most widely recognised spongiform encephalopathy of animals is scrapie, which is a fatal progressive neurological disorder of sheep. Scrapie has been reported from many countries of the world and has been recognised in British sheep flocks for over two centuries, having been first recorded in 1732. It affects sheep and goats naturally and can be transmitted experimentally to several animal species, particularly mice, after which the disease may be passaged in that species with a significantly reduced incubation period. There are a few records of similar encephalopathies arising naturally in animals such as a transmissible encephalopathy in mink (Mustela vision) (26), chronic wasting disease in captive mule deer (Odocoileus hemionus) and a spongiform encephalopathy in a sub-species of the red deer, the Rocky Mountain elk (Cerus elaphus sibiricus nelsoni) in captivity (53,54). None of these diseases has been reported in similar species, captive or wild, in this country. Transmissible mink encephalopathy (TME) is believed to have arisen as a result of feeding raw sheep offal to ranched mink.

Transmission of the scrapie agent occurs naturally between sheep. Both maternal and lateral transmission is recognised (14) though the precise mode of transmission is not known (29) [see para 5.1.2]. Clinical disease does not generally appear until sheep are between 2.5 and 4.5 years of age. Affected sheep show behavioural changes such as intense itching (hence the name scrapie) and incoordination which progresses to an inability to stand and eventually death. Antibodies to the scrapie agent have never been detected and no test which will confirm the presence of disease during life has ever been discovered.

Brain changes are predominantly degenerative, the main feature being cell vacuolation. There is neuronal loss and gliosis. Another feature of scrapie, and all spongiform encephalopathies, is that inflammatory reaction is minimal or absent. In addition, abnormal fibrils, "scrapie associated fibrils" (SAF), can be detected in infected brain extracts with the electron microscope (39). The presence of these fibrils is now recognised as one identifying feature of the spongiform encephalopathies. Molecular studies of the fibrils from the brains of cattle affected with BSE have shown that they contain the same type of glycoprotein as is present in SAF (28). The pathological changes in hound ataxia and feline dysautonomia are quite different from those of the spongiform encephalopathies.

Strain variations of the scrapie agent have been recognised from mouse studies on the basis of pathological and biological properties (12). An unusual feature of the agent is its remarkable resistance to inactivation by a wide range of physical and chemical treatments such as ultra-violet light and formalin (23,16) [see para 3.9]. Although scrapie is caused by an infectious agent the expression of the disease depends on host genetic factors (15).

3.3 Human spongiform encephalopathies

Kuru, Creutzfeldt-Jakob Disease (CJD) and its even rarer variant, the Gerstmann-Sträussler-Scheinker (GSS) disease, are spongiform encephalopathies described in man. Like the animal disorders, they are progressive and universally fatal. Kuru is a spongiform encephalopathy that at one time was common in certain tribes in New Guinea, although not recognised elsewhere. Transfer of infection by the subviral pathogen was thought to occur through ceremonial handling and ingestion of human brains affected by the disease (21). As the disease is not vertically transmitted, the incidence of Kuru has decreased dramatically since these practices ceased around 1956, although several cases still occur each year in patients over 30 years of age; this is
consistent with an incubation period of 30 years or more (2).

3.4 Although a rare disease, occurring at an incidence of around 0.5 to 1.0 case per million per annum, CJD has been the subject of extensive study and the possibility of a relationship with scrapie explored. A small number of cases can be attributed to iatrogenic transmission from other cases of CJD through the transplantation of nervous tissue and corneas, and the use of brain electrodes and human growth hormone (44). In the majority of cases of CJD, the source of infection cannot be determined. Familial cases are a small minority (generally under 10%\(^*\)) and there is little support for direct case-to-case transmission. The epidemiology suggests that CJD is a disorder of minimal infectivity with an as yet undetermined route of transmission and a long incubation period: current evidence, from the small number of cases that have followed growth hormone treatment, is of periods up to 20 years. This group of cases also suggests that symptomless persons may exhibit pathological features in the brain tissues. The much more common dementia, Alzheimer's disease, is not considered one of the spongiform encephalopathies, for although there are several overlapping properties (33,34), it is not generally regarded as transmissible.

3.5 Investigation of possible association between animal and human spongiform encephalopathies

Over the years, various studies have been conducted in order to explore the possibility that scrapie in sheep might be a source of CJD in humans (4,24,11,7). These include studies designed to examine tentative associations between sheep and CJD. In one of the most recent studies (7), a total of 329 patients was identified in France between 1968-1982 as having died of CJD. On the link with scrapie, the authors wrote:-

"Conflicting evidence has been accumulated in our study about the possibility that scrapie in sheep might be a source of CJD in humans. Although two of the patients in this series were shepherds, no case of CJD occurred in any other occupational group in direct contact with sheep carcasses or products. The regional distribution of CJD was unrelated to the location of scrapie-infected flocks of sheep, or to the commercial destinations of lamb from areas in which scrapie was endemic. In one endemic area, we were unable to isolate scrapie virus from either brain or visceral tissue taken from lambs and ewes selected at random in a centrally located slaughter house. The high incidence of CJD found in Algerian and Tunisian immigrants could have been either genetically determined, or the result of early environmental viral contamination, including youthful exposure to the heavily sheep-oriented North African cuisine" (7).

3.6 In studies of the worldwide incidence of CJD, associations with eating sheep brain or eyeballs have been described (4,11), but transmission by the oral route from sheep is not supported by other evidence, including a case control study in Libyan Jews (24). There are obvious difficulties in relating a disease with a very long incubation period to dietetic habits. CJD occurs at its usual frequency in Japan where scrapie is very rare and Australia where it has never been recorded; CJD has also been reported in a lifelong vegetarian (7).

3.7 Scrapie has been endemic in Great Britain for centuries without there being any evidence to show an incidence of CJD higher than the international average in the human population (37).

\(^*\) except in Chile (27\%) (22) and Czechoeslovakia where up to 35% of cases in the rural population are familial (38)
3.8 Transmission of BSE to mice

Mice inoculated with brain homogenates from two separate BSE cases have, after 10–11 months, shown signs of an encephalopathy (20). The histopathological changes observed are indistinguishable from those produced in mice following primary transmission of sheep scrapie. Four different strains of mice were used; signs so far have been seen in two strains (RII, C57) with the observed difference in the median incubation period in these two strains being 80 days. Studies are in progress to determine whether this difference in expression in the strains of mice can be accounted for by differences in the doses administered or whether, as with scrapie, sensitivity to the expression of the disease varies with the host genotype.

3.9 Destruction of agents of spongiform encephalopathies

The agents responsible for the spongiform encephalopathies show unusual resistance to the processes that are usually used to inactivate infectious organisms such as wet and dry heat, ultra-violet and ionising radiation (3), alkylating agents, organic solvents, concentrated salt solutions and many detergents (23, 16). Although any exposure to temperatures over 100°C will lead to some loss of infectivity (46), in various experiments complete loss of the infectious agent was not achieved by heat at 121°C for 1 hour (scrapie) or 240°C for 1 minute (scrapie and CJD) (8) or 126°C for 1 to 2 hours (scrapie) (31). Some strains of agent (eg 22A scrapie) are more heat-resistant than others. The current recommendations for sterilisation procedures for infected equipment contaminated by patients with CJD is, for the autoclaving of a porous load, a single cycle at 134-138°C (30 lbs psi) for 18 minutes hold time or six separate cycles at 134-138°C for 3 minutes hold time each. Formalin fixation appears to increase heat-resistance of scrapie agent (50) and the current recommendations may be inadequate under these circumstances.

Scrapie and CJD agents have also been shown to be resistant to various chemical disinfectants, although higher concentrations (at least 2% available chlorine) of sodium hypochlorite may be effective in at least reducing the titre if contact is maintained for 30 minutes or more (31) as may immersion in 1.0 N sodium hydroxide for 1 hour at room temperature (8).

3.10 In summary, the present state of knowledge shows that all these diseases have similar pathologies with spongiform change in the central nervous system and with abnormal fibrils identified ultrastructurally; they also produce similar EEG abnormalities; they are inevitably fatal and the causal subviral agents are not destroyed by normal sterilisation processes. The period from infection to the expression of signs is long (in relation to the life span of the animal), eg from ten to eleven months for BSE in mice to as much as 30 years for Kuru in humans. The agents may be transmitted by direct injection into the nervous system, by transplantation of tissues or, in humans, injection of hormone derived from human sources; some transmission is almost certainly oral (Kuru, scrapie to cattle giving BSE, and scrapie to mink giving TME), but the usual mode of transmission of the most widespread disorders (scrapie and CJD) is unclear. Expression of these disorders may also be influenced by host genotype.

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DA(84)16 DHSS circular “Management of Patients with Spongiform Encephalopathy (CJD)”
4. THE CAUSE OF BOVINE SPONGIFORM ENCEPHALOPATHY: THE EPIDEMIOLOGICAL EVIDENCE

4.1 Methods

4.1.1 The Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food has been undertaking an epidemiological study to determine the cause of the disease (52). A comprehensive questionnaire is being used to obtain epidemiological data about herds which have had one or more confirmed cases. The information obtained includes the date of birth, breed, sex, herd of origin (if purchased), breed society herd book number and pedigree records (where appropriate), date of clinical onset and stage of pregnancy at onset, the identities of offspring and the presence or otherwise of specific clinical signs. Specific descriptions of the presenting signs and progression of the disease are also obtained from the herdsmen and veterinary surgeons.

4.1.2 In addition, information has been obtained in relation to the herd type, size and age structure, whether or not there have been sheep on the farm since 1980, the destination of animals sold and the origin of breeding animals since the birth of the initial case, and details of the use of pharmaceutical products, vaccines, pesticides and herbicides. Feeding practices since the birth of the initial case are also determined.

4.1.3 A computer simulation model has been constructed on the hypothesis that BSE is caused by an unconventional transmissible agent. It was designed to examine the time of onset and duration of exposure, the incubation period, distribution and age classes of animals exposed. The model consists of a large population of calves, young stock and adult stock. The latter have been subjected to a specific culling rate obtained from previous studies of dairy herds. Values for the exposure parameters and incubation period have been imposed on the model. The incubation period is assumed to have a log normal distribution, and to exhibit no variation with age at first exposure. The age specific incidences of BSE in herds with confirmed cases are used to assess the validity of the exposure and the incubation period parameter. The simulation is also used to predict changes in age specific incidences in future years [see para 4.2.7].

4.1.4 The complete herd breeding records obtained from one multiple case herd have been analysed to examine the hypothesis that BSE is the result of an autosomal mode of inheritance. For this, the pedigrees of all confirmed cases in Great Britain, accumulated to the end of 1988, have been used to produce a list of putative heterozygous carrier bulls, ie the sires or maternal grandsires of confirmed cases. This provides for the identification of animals from the specified herd whose sire and maternal grandsire were putative heterozygous carriers (52).

4.2 Results and Conclusions

4.2.1 The epidemiological picture, as shown by the distribution of cases by month and year of onset, is shown in Figure 5. It is typical of an extended common source epidemic. Movement of cattle between known affected herds does not account for the occurrence of cases and the initial cases in different herds developed clinical signs within a relatively short period of each other. All affected animals therefore appear to be index cases. No evidence of cattle-to-cattle transmission has yet been observed. The age of the confirmed cases ranges from 3 to 11 years and their year of birth from
1979 to 1984. BSE had been confirmed in 4 bulls by the end of December 1988. The incidence of affected dairy herds increases directly with the herd size: 75% of herds have only experienced single cases. The high incidence of affected herds in the South of England suggests that there is a true regional variation in risk.

4.2.2 Cases have been studied in detail to seek a common factor in terms of treatments given to calves, young stock or the adult herd. The use of organophosphorus fly sprays, systemic pyrethroid sprays, synthetic pyrethroid ear tags (for fly control) and organo-phosphorus warblecide have not been shown to be a common factor. Newly introduced vaccines such as those for leptospirosis have been used only in a very small proportion of herds. There is therefore no evidence for the introduction of a novel infectious agent through a particular biological product. Similarly, other pharmaceutical products that have been introduced relatively recently eg anthelmintics and "reproductive hormones" and the use of weedkillers/herbicides and pesticides are not common factors. The absence of any association at the time of onset of clinical signs with either month or state of pregnancy/lactation was not consistent with an acute toxic effect of pharmaceutical products or agricultural chemicals, the use of which is usually restricted to particular months or seasons or to specific times in an animal's lifespan or reproduction cycle. Genetic studies have revealed that while some familial relationships between affected cattle in a small number of herds have been found, there is positive epidemiological evidence that excludes BSE from being exclusively a simply inherited disease. There is also no evidence that BSE has been introduced by imported cattle or semen. Finally, the transmission of the scrapie agent from sheep to cattle via direct or indirect contact on the affected farms appears to be an untenable hypothesis in view of the absence of sheep on 20% of the farms concerned.

4.2.3 The only common feature in all the cases that have been investigated is the use of commercial concentrates, either as finished rations, such as pelleted calf feed and dairy calf cake, or protein supplements used in home mixed rations. This points to meat and bone meal as being the vehicle of infection. Studies are continuing in order to try to determine more precisely the exposure of the affected and unaffected animals to meat and bone meal in commercial concentrates*. Meat and bone meal is distributed, and incorporated into animal rations, within a relatively small radius of its production, compared with tallow. The geographical variation in incidence indicates a geographical variation in risk which is not consistent with the distribution and use of tallow. In addition, in the rendering process the BSE agent would probably partition with the cellular residues of the meat and bone meal fraction, rather that with the lipids of tallow. The feed-borne hypothesis is also supported by the considerably greater incidence in dairy herds compared with beef suckler herds as there is a reduced rate of concentrate feeding, particularly with calves, in the latter herd type. 3.6% of dairy herds have been affected, whereas only 0.12% of beef suckler herds. The positive association between herd size and the risk of occurrence of a case of BSE is likely to be due to an increase in the probability of purchasing an infected batch of food with increasing herd size.

* There are a number of formulations of proprietary concentrate rations for cattle. Concentrate rations for calves are produced in pelleted form and referred to as pellets, pellets or nuts and in a non-pelleted form referred to as a coarse mix. Pelleted concentrates for adult cows, particularly dairy cows, are the commonest formulation fed and these are referred to as cake, nuts or merely concentrates.

1600 out of 44782 dairy herds and 67 out of 54368 beef suckler herds up to 31 Dec 1988. There are around 1.9m adult beef cows and 2.1m adult dairy cows in Great Britain.
4.2.4 The occurrence of TME in ranch-reared mink, first recorded 40 years ago, seems to be a precedent for the food-borne transmission of the agent. The source of the infection in ranched mink in the USA was attributed to the feeding of scrapie-infected sheep or goat tissues (35). It is also interesting to note the occurrence, in a wildlife park in the UK, of a spongiform encephalopathy in a nyala (*Tragelaphus angasi*)* in June 1986 and a gemsbok (*Oryx gazella*)* in July 1987. These animals had no contact with each other and no source of a transmissible agent was evident at the time these cases were investigated. However, from March 1986 to March 1987, they were fed a commercial concentrate which included meat and bone meal. This ingredient was believed not to have been incorporated into the feed for 11 years prior to March 1986. If this is correct, then the disease presented in these species surprisingly rapidly.

4.2.5 The reason for the geographical variation in BSE incidence has not been firmly established, but studies are continuing. It can not be explained simply by the geographical variation in dairy herd size distribution. One hypothesis is that it mirrors the geographical variation in the market share of cattle feedstuffs between the major compounders assuming that there is a variation between companies in the use and inclusion rate of meat and bone meal. There is some evidence that this explains the apparently anomalous difference in incidence between Guernsey and Jersey.

4.2.6 In every case of BSE investigated so far, animal protein had been fed to the animal. Herds that are at present free of the disease have also been investigated and most of these have been fed rations containing animal protein. However a small number of herds (under 3%) has been identified where this has not occurred and none of these animals has developed the disease. This study is continuing.

4.2.7 The use of a computer based simulation model indicates that the values of the age specific incidences which have been observed are consistent with the following features. Firstly, both calves and adults (over 2 years of age) were exposed, but the risk of clinical disease was 30 times greater for calves than for adults. Secondly, an incubation period occurred with a range from 2.5 years to at least 8 years and a log normal distribution. The maximum incubation period that could have been observed in 1987 was 6 years (52). Thirdly, exposure of the cattle population commenced in the winter of 1981/82 and continued until at least the end of 1985. Further epidemiological data are needed to demonstrate that exposure and infection continued beyond 1985, but it seems likely that this was so until July 1988 [see 6.1].

4.2.8 There is no clear or single explanation why it appears that in 1981/82 cattle apparently first became exposed to an agent sufficient to result in clinical disease. On the other hand a number of factors have been identified which, combined, could be important in the occurrence of this epidemiological phenomenon. These include a significant increase in the sheep population in Great Britain which commenced in 1980 and has continued since; a possible increase in the prevalence of scrapie infected flocks; the greater inclusion of sheep heads in material for rendering; the greater inclusion of casualty and condemned sheep in material for rendering as a result of the reduction in the number of knackers' yards; the introduction of continuous rendering processes during the 1970s and 1980s, which may have resulted in the rendering of animal material at a lower temperature and/or for less time than previously [see appendix 1], and the decline in the practice of using hydro-carbon solvents for fat extraction since the mid-1970s. These factors provide a possible explanation for a change in exposure of cattle to ovine-derived protein and thus the scrapie agent (52,40,5).

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*African antelopes*
4.2.9 A further hypothesis to explain the occurrence of BSE is the emergence or selection of a strain or strains of the scrapie agent pathogenic for cattle. Mutations of the scrapie agent, which can occur after a single passage in mice, have been well documented (9). This phenomenon cannot be dismissed for BSE, but given the form of the epidemic and the geographically widespread occurrence of BSE, such a hypothesis would require the emergence of a mutant scrapie strain simultaneously in a large number of sheep flocks, or cattle, throughout the country. Also, if it resulted from a localised chance transmission of the scrapie strain from sheep to cattle giving rise to a mutant, a different pattern of disease would have been expected: its range would have increased with time. Thus the evidence from Britain is against the disease being due to a new strain of the agent, but we note that in the United States from 1984 to 1988 outbreaks of scrapie in sheep flocks are reported to have increased markedly, now being nearly 3 times as high as during any previous period (18). From enquiries we have made, it seems unlikely that any bone meal for cattle food has been imported into Britain from the USA.

5. THE TRANSMISSION OF BOVINE SPONGIFORM ENCEPHALOPATHY

5.1 In cattle

5.1.1 The epidemiological studies carried out so far have not revealed any evidence of vertical (dam to offspring) or horizontal (bovine to bovine) transmission of disease. Neither is there any evidence of transmission via semen or embryos. Over 300 offspring of cows in which BSE has been confirmed, together with the same number of control animals, are being monitored by the Ministry of Agriculture, Fisheries and Food's Central Veterinary Laboratory [see para 8.1]. The Laboratory is also undertaking research projects into the possible means of transmission. The occurrence and incidence of maternal transmission, should it occur, will probably not be evident from the field epidemiological study until after 1990.

5.1.2 Field observations and experimental work have established that there is transmission of scrapie from the infected ewe to the lamb. Various experiments have been carried out involving the transfer of fertilised embryos from scrapie-infected ewes to scrapie-free ewes and vice versa. From these and other studies it is concluded that the scrapie agent is not present in semen, in the very young embryo or the lamb at the time of birth (19,18). The placenta is highly infectious (41) and is the most likely source of infection for the new born lambs. Although the disease in goats behaves in a similar way to that in sheep, some species, such as rodents and mink which are susceptible to scrapie, act as dead-end hosts with no direct animal to animal transmission. At the present stage of knowledge it is impossible to predict whether cattle to cattle transmission of BSE will occur.

5.2 To other non-human animals

5.2.1 The concept of a "species barrier" in relation to scrapie has been the subject of discussion because of the variation in the success rate of primary transmissions of scrapie to other species. Two reasons, apart from variation in the doses of agent administered, have been suggested. These are firstly that the strain of agent is unable to reach replication sites in the new host either because of its essential structure or because of some phenomenon involving donor tissues with which it happens to be associated. The second is that the agent in question fails to replicate even though it can reach sites in the recipient at which other strains of the agent
replicate. Even if these reasons do not apply it may be that replication of the agent is so slow, or the initiation of replication is so delayed, that disease does not occur during the new host’s lifespan (21).

5.2.2 As mentioned above in 4.2.4, signs identical to those of a spongiform encephalopathy have already been described in two antelopes both of whom were fed meat and bone meal-containing rations. BSE has also been transmitted experimentally by intracerebral inoculation into mice (20). In theory other animals may have been exposed to the BSE agent, and there is a risk that this might occur in the future. Concern here arises not only for the health of the animals concerned, but in case other species might act as sources of yet further spread.

5.2.3 Since no natural infections have ever been described in non-mammalian species it seems unlikely that they would be susceptible to BSE, scrapie or any other spongiform encephalopathy. It may be noted, though, that poultry feed frequently contains both bovine and sheep tissues. Without specific tests for the agents concerned, it cannot be proven that poultry are unable to carry the agent in an infectious form, but it is considered that the chance of this is so small, and the risk were this to occur so remote, that no action is appropriate at this stage. However, if a specific test were to be developed, research on the agents of spongiform encephalopathies in non-mammals, including poultry, should be undertaken.

5.2.4 Other mammals exposed to sheep and bovine material include domestic pets and mink. Encephalopathy in mink is likely to present as TME but to date there have been no cases in the small UK mink population. There are no descriptions of naturally occurring spongiform encephalopathies in domestic pets such as cats and dogs. Even in the absence of any natural disease, domestic pets could well be susceptible to BSE were the agent to reach them in an adequate dose by an appropriate route. Whilst pet food frequently contains offal from both sheep and cows, so that the source material must have contained scrapie and possibly BSE agents, there is no evidence of relevant neurological disease in cats or dogs. It seems unlikely, but possible, that preclinical infection exists but is not revealed because of an incubation period longer than the natural lifespan. On the other hand, it may be that infection cannot be acquired orally by these species or that the high temperatures used in pet food canning destroys any infectious agent [see para 3.9]. Nevertheless, transmission experiments in cats and dogs and surveillance of the health of domestic pets are items that should be brought to the attention of the Consultative Committee on Research and the veterinary profession. Hounds that are often fed uncooked carcasses would be particularly appropriate for study. Other ruminants, principally various deer and antelopes, would clearly be at considerable risk of developing this disorder if, contrary to current regulations, fed material with bone meal and meat residues from sheep or cattle.

5.3 Possible Transmission to Man

5.3.1 Kuru and Creutzfeldt-Jakob Disease demonstrate that humans are susceptible to spongiform encephalopathies. The potential routes of transmission of BSE from cattle to humans have been examined closely. With the very long incubation period of spongiform encephalopathies in humans, it may be a decade or more before complete reassurance can be given.

5.3.2 Information from several spongiform encephalopathies suggests that parenteral inoculation is much more efficient in transmitting disease than oral or topical exposure and that neural, and to a lesser extent, lymphoid tissue carry the infection whilst the risk is far less with other tissues. The theoretical routes of
transmission from cattle to humans can be presented in "risk" order to help clarify whether action is appropriate or research worthwhile.

5.3.3 The greatest risk, in theory, would be from parenteral injection of material derived from bovine brain or lymphoid tissue. Medicinal products for injection or surgical implantation which are prepared from bovine tissues, or which utilise bovine serum albumin or similar agents in their manufacture, might also be capable of transmitting infectious agents. All medicinal products are licensed under the Medicines Act by the Licensing Authority following guidance, for example from the Committee on Safety of Medicine (CSM), the Committee on Dental and Surgical Materials (CDSM) and their sub-committees. The Licensing Authority have been alerted to potential concern about BSE in medicinal products and will ensure that scrutiny of source materials and manufacturing processes now takes account of BSE agent.

5.3.4 Direct inoculation of bovine tissue could also occur accidentally in certain occupations, such as slaughtermen, veterinarians and laboratory workers. Guidance on safe working practices in general are drawn up by the Health and Safety Executive who have been alerted to the potential concern about BSE and in particular to the possible infectivity of placentae. No specific additional guidance on BSE is thought appropriate at this time. However adherence to recommended procedures in handling animals and animal products is clearly very important.

5.3.5 In these, as in other circumstances, the risk of transmission of BSE to humans appears remote. Nevertheless, because the possibility that BSE could be transmitted orally cannot be entirely ruled out, known affected cattle should not enter the human food chain and action now undertaken ensures this. What evidence there is does not suggest that milk can transmit any of the spongiform encephalopathies. Nevertheless, to be consistent with the earlier recommendation that cattle known to be infected with BSE should not be offered for human consumption, we have recommended that milk from cows suspected as having BSE should be destroyed. Action has also been taken here. Finally if the BSE agent were to be present in an animal it is most likely to be in the spleen and lymphatic tissues in the early stages of infection, and as the disease progresses in the brain and neural tissue (17,13,32). It has been suggested, although clinically affected cattle are being slaughtered and destroyed, that consideration should be given to products containing brain and spleen being so labelled, to enable the consumer to make an informed choice (27). The Working Party believes that risks as at present perceived would not justify this measure. We note that current regulations that require contents of processed food to be listed permit the generic terms "meat" and "offal". We consider that manufacturers of baby foods should avoid the use of ruminant offal and thymus; the latter can currently be described on food labels as meat.

5.3.6 It is a reasonable assumption that were BSE to be transmitted to humans, the clinical disorder would closely resemble CJD. Depending on the route of transmission, the incubation period could be as little as a year (as with some iatrogenic CJD cases) or several decades (as estimated for many natural CJD cases). Identification of any such cases as unusual or atypical would not be easy. However the Chief Medical Officer could consider whether specialist branches of the medical profession such as neurologists, neuropathologists and neuropathologists, to whom cases of suspected CJD are referred for diagnosis, should be made aware of the emergence of BSE so that they can report any atypical cases or changing patterns in the incidence

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1 The Food Labelling Regulations 1984 (S.I. 1984 no 1505) and The Meat Products and Spreadable Fish Products Regulations 1984 (S.I. 1984 no 1566)
of disease. CJD also remains of considerable interest to epidemiologists and they should also be advised to watch for any changing patterns in relation to the disease. The Office of Population Censuses and Surveys is already reviewing deaths attributed to CJD and will be looking for any trends or particular occupational or other characteristics in the deaths certificated to CJD. The questions of specific monitoring of population groups considered at enhanced risk of BSE exposure, or more detailed surveys of CJD cases, are included amongst those to be referred to the Consultative Committee on Research.

6. THE FUTURE COURSE OF THE DISEASE

6.1 Estimate of number of future cases

As indicated above in 5.1.1 there is no evidence of maternal or horizontal transmission of BSE. If these methods of transmission are assumed not to occur it is possible to make an estimate of the order of magnitude of future incidence. The results of the epidemiological study so far indicate that exposure was not for a discrete short period, but from 1981/82 until at least 1985 and assumed from then until 18 July 1988 when legislation was introduced to prohibit the inclusion of ruminant-derived protein in ruminant feedstuffs [see paragraph 7.1.1]. There are however three factors which may have affected the exposure of cattle to the BSE agent since 1985. First, the introduction of milk quotas in 1984 resulted in lower rates of concentrate feeding to dairy cows and therefore a reduced exposure for adult animals; this is unlikely to have a significant effect as the majority of animals have been infected as calves. Secondly, as a result of the continuing increase in the sheep population, the proportion of ovine material entering rendering plants will have increased. Thirdly, the inclusion of infected cattle into the cattle food chain until 18 July 1988 could have increased the exposure. The effects of the latter two factors are impossible to quantify, but could be minimal and undetectable, resulting in essentially a constant exposure. If this is the case, and given the incubation period distribution, then a constant number of cases, of the order of 350-400 per month, can be expected; this is an incidence of 1 case per 1,000 adult cows per year. If the age structure of the national adult herd remains constant, as the usual life span of a milk cow in Great Britain is at present 5 to 6 years this rate of presentation of the disease will continue until 1993, a cumulative total of about 17000-20000 cases from cows currently alive and subclinically infected. Thereafter, if cattle to cattle transmission does not occur then a reduction in incidence would follow with a very low incidence in 1996 and the subsequent disappearance of the disease.

6.2 Estimated new infections in cattle

The estimates in 6.1 assume that no new infections have arisen or will arise after 18 July 1988 when the ban on ruminant protein in feed became operative; this ban is to continue unless processing in rendering plants is shown to be adequate to inactivate scrapie agent [ see 7.1.2]. No allowance has been made for new infections arising from lateral transmission in cattle; there is no evidence from the available epidemiology that this has taken place [5.1.1] and evidence from other spongiform encephalopathies suggests it will be unlikely. No allowance has been made either for new infections arising from maternal transmission: insufficient time has elapsed to determine whether maternal transmission occurs in BSE and if so at what incidence. Given the age distribution of the BSE cases at the onset of clinical signs and therefore the number of offspring which will survive the minimum incubation period, the occurrence of maternal transmission, should it occur, is unlikely to be witnessed
until 1990.

Though maternal transmission would increase the number of cases on its own it would probably be insufficient to sustain BSE in the national cattle population because it is likely that the number of offspring per case which will reach a susceptible age and produce their own offspring will be less than one. If transmission does occur this is most likely to be from the placenta and membranes, as in scrapie [para 5.1.2]. Environmental contamination from this source may be more readily controlled in cattle herds than in sheep flocks because of the differences in management, and we suggest that in those herds where the disease has occurred attention should be given to the rapid collection and destruction of placentae.

6.3 Estimate of BSE in other species

As mentioned in 4.2.4, BSE has been seen in a wildlife park. It is not known how widespread the practice of feed supplementation of animals in zoos and game parks has been but several species may be susceptible to BSE [see 3.2] and limited new infections with BSE could arise. The possibility of transfer to other species is discussed in 5.2 and 5.3. It cannot automatically be assumed that animals and man will react to BSE agent exposure as they have done to scrapie, which in the human case has not led to any clear association with disease [see 3.5 to 3.7]. BSE agent may for example be an adapted or particularly virulent form of scrapie agent although the results of the epidemiological study indicate otherwise [see 4.2.9].

6.4 Zoonoses

Zoonoses are diseases of animals which present a risk to human health through a pathway of infection. Many diseases have arisen in this way for a large number of pathogens can infect man as well as animals (49). Brucellosis and bovine tuberculosis (TB) are examples that have been of great concern in the recent past in Great Britain. At present the common zoonoses in Britain are salmonella, listeria and campylobacter food-poisoning. Changes in the habits of humans lead to the opening up of new pathways of infection and predispose to the emergence of new zoonoses. The increased efficiency of modern agriculture has in part been achieved by its intensification and by short-circuiting natural pathways, as, for example in recycling animal waste, i.e. feeding animal waste to chickens, cattle and pigs. Such procedures have many advantages: they reduce the loss of nutrients and they increase the growth or output of the animals, whilst at the same time disposing of waste materials that are themselves potential health hazards and pollutants. However ruminants are not by nature scavengers, thus unlike hyaenas, foxes or vultures they will not have evolved defences against the transfer of pathogens from animal wastes; as the Royal Commission on Environmental Pollution warned in its 7th Report (47) "the major problem encountered in this recycling process is the risk of transmitting disease-bearing pathogens to stock and thence to humans" (para. 5.63). Some recent zoonoses, like bovine TB and brucellosis, have been controlled but strict measures are often needed to eliminate the risk to humans from these animal disorders.
7. ACTIONS ALREADY TAKEN TO REDUCE SPREAD OF DISEASE

7.1 Feed Prohibition

7.1.1 In the light of the findings of the epidemiological study the Government indicated in May 1988 that it would introduce legislation (the Bovine Spongiform Encephalopathy Order 1988) which would prohibit the sale, supply or feeding of rations containing animal protein, derived from ruminants, to cattle and other ruminant animals. This action was greatly welcomed by the Working Party which had just been established. The order became effective from 18 July 1988.

7.1.2 Legislation (The Bovine Spongiform Encephalopathy (No. 2) Order 1988) has since been introduced which extends the prohibition on the use of ruminant-based feed for a further year i.e. throughout 1989. Based on a survey of the processes operated in rendering plants in Great Britain, and the available data on the activity of “unconventional agents” after various heat treatments [Appendix 1 and para. 3.9], we consider that there is no way of being wholly sure that rendering as practised would eliminate the agent. Accordingly we recommended that the ban on the use of ruminant-based protein in ruminant rations be extended indefinitely believing that this would indicate to the industry that there can be no return to unmodified earlier practices. The original prohibition was time-limited from 18 July to the end of 1988. The Government decided that rather than make the ban indefinite, as the Working Party recommended, it would be preferable to extend it for a year. During this time further consideration will be given to the time/temperature combinations which are necessary to destroy the agent which causes BSE. If these can be determined it may be possible by adapting some of the previous rendering processes to produce a safe product. On this issue the Working Party were reassured by the Minister's statement that the prohibition would have to continue beyond the end of 1989 unless processing methods which are sufficient to destroy the agent have been identified and are widely available. The Working Party wishes to emphasise the need to be completely confident that the agent has been destroyed and must point to the difficulties of demonstrating this in view of the nature of the agent and the time taken for the symptoms to manifest themselves, even in the mouse model [see 3.8 and 3.9].

7.2 Destruction of carcasses of cattle affected with BSE

7.2.1 On 7 July 1988 the Ministry of Agriculture, Fisheries and Food announced that a compulsory slaughter-with-compensation policy would be introduced following the interim advice from the Working Party. The new arrangements came into force on 8 August 1988. Under them, cattle with a clinical picture of BSE are compulsorily slaughtered and disposed of either by incineration or burial. Before disposal the head is removed so that the brain can be examined to establish a definitive diagnosis.

7.2.2 Compensation is paid at 50% of the market value of the animal, as if it were not affected with BSE, up to a ceiling. Should the disease not be confirmed following examination of the brain tissue, 100% compensation is paid. The legislation covering compulsory slaughter and the payment of compensation is contained in the Bovine Spongiform Encephalopathy (No 2) Order 1988 and the Bovine Spongiform Encephalopathy (Compensation) Order 1988.
7.2.3 It has been suggested that because compensation is set at 50% some farmers are evading the law and that as a result the carcases of affected animals are reaching the human food chain. However the evidence does not support this view. The number of suspect cases being reported has gone up since the compulsory slaughter programme was introduced. It also seems likely that should a farmer try to sell an animal for slaughter, rather than report suspected BSE, the transportation to a market and abattoir will exacerbate the clinical signs of the disease [2.3]. In these circumstances the animal will probably be reported at the market or slaughterhouse through surveillance. In fact from 21 June 1988 to the end of the year BSE was confirmed in only 40 out of a total of 63 suspect cases reported from markets and slaughterhouses. None of these cases was from herds in which BSE had previously been recognised: so there was no evidence that early signs had been suspected and that evasion was deliberate.

7.3 Milk from Cattle with suspected BSE

Although the transmission of BSE via milk is very unlikely, indeed milk has never been shown to be able to transmit any of the other spongiform encephalopathies, the working party recommended at its second meeting that as a precautionary measure the milk from cattle in which BSE was suspected should be destroyed. The Government accepted this recommendation. Legislation (The Bovine Spongiform Encephalopathy (No. 2) Order 1988) came into force on 30 December 1988 prohibiting the sale or use of milk from suspect animals for human or animal consumption, the exception being for the feeding of the cow’s own calf. The exception is made in view of the practical and welfare problems which could well arise should there be a legal requirement to remove the calf at the time of birth.

8. FURTHER RECOMMENDATIONS

8.1 Monitoring of offspring of affected animals

The eventual size of the BSE epidemic [see section 6] will depend very largely on whether or not the cow is a dead-end host. If this is the case, and the action taken as described in 7.1 and 7.2 has stopped new infections, the disease should die out as the cohorts of infected animals develop BSE and are destroyed. It is essential that enough offspring of cows known to have had or to have subsequently developed BSE are monitored to enable evidence for or against vertical transmission to be obtained. Three hundred such offspring with an equivalent number of controls have been identified by the Ministry [see 5.1.1]: the Working Party urge that all necessary resources are made available to ensure that these animals are monitored and that they are not destroyed before they are old enough to display the disease, should they be infected. Premature loss of these animals could delay for some years acquisition of evidence about vertical transmission in cattle.

8.2 Medicinal Products

Consideration has been given to the potential for the transmission of BSE between cattle and other species, including man, through the use of medicinal products [see paragraph 5.3.3]. Although the risks appear remote the Working Party recommended that the attention of the Licensing Authority, the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials and the Veterinary Products Committee (VPC) be drawn to the emergence of BSE so that they can take appropriate action. In this connection the Chairman of the Working Party has corresponded with the Chairman.
of the CSM and with the VPC [Appendix 3].

8.3 Health and Safety

Paragraph 5.3.4 draws attention to a number of occupational groups, such as veterinarians, slaughtermen, herdsmen and laboratory workers, who could conceivably be exposed to the BSE agent. It is recommended that the potential problems caused by BSE are brought to the attention of the Health and Safety Executive who can consider whether further guidance should be given to such groups.

8.4 Surveillance

Monitoring of cases of Creutzfeldt-Jakob Disease should take place, both through the neurological network and by OPCS, since any human cases of BSE would present as CJD [see para 5.3.6 above].

8.5 Research

8.5.1 The Working Party has discussed a number of areas of research which it considers essential if progress is to be made in our understanding about the disease and how to deal with it. In the first interim report from the Working Party we recommended that a new committee should be set up to advise, co-ordinate and oversee the research work needed in this field. This recommendation has been accepted. An expert Consultative Committee on Research has now been established. The membership is:-

Dr D Tyrrell CBE, FRS - Director MRC Common Cold Unit (Chairman)

Dr W A Watson - Director of the Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food

Professor J Bourne - Director of the Institute of Animal Health

Dr R J Will - Consultant Neurologist at the Western General Hospital, Edinburgh

Dr R Kimberlin - Ex-Director of the Neuropathogenesis Unit Edinburgh

Its terms of reference are:-

1. "To advise the Ministry of Agriculture, Fisheries and Food and Department of Health on research on transmissible spongiform encephalopathies including:-
   a. work already in progress or proposed;
   b. any additional work required
   c. priorities for future relevant research.

2. In the context of these terms of reference transmissible spongiform encephalopathies includes those affecting both domestic and wild ruminants and man".
8.5.2 Areas of research which this Working Party believes should be considered are:

(i) Epidemiological Studies - in particular to examine further the role of meat and bone meal as the source of BSE and to determine whether or not maternal (vertical) and horizontal transmission can take place.

(ii) Transmission studies in a variety of possible host species. Transmission to mice has already been demonstrated at the MRC/AFRC Neuropathogenesis Unit. We understand that other studies are underway or planned using cattle, marmosets, hamsters, mink and goats. Parallel cattle studies are also planned using the scrapie agent. Further projects are planned, using material from affected cattle, to determine whether or not transmission is possible via semen and embryos. Follow-up studies should be designed to determine the physical and chemical processes to which the agent is susceptible and thus the conditions required to make material (such as rendered infected carcases) "safe".

(iii) Transmission experiments using muscle and milk, in the latter case to repeat earlier experiments which showed that milk was not a vehicle for scrapie transmission to any species.

(iv) Possibility of formal monitoring of the health of pigs and domestic pets, particularly since pigs are used in the manufacture of some pharmaceuticals. Transmission experiments may be relevant for some of these species. We assume that there is no intention to exclude these animals from the Committee's terms of reference, and believe that the departments concerned will recognise the dangers of excluding these potential infective pathways.

(v) Studies to determine whether the BSE agent is identical in its molecular structure to the natural agent of scrapie or modified in some way. Determine whether there are single or multiple strains and the relationship to agents responsible for transmissible encephalopathies in other species.

(vi) The determination of the nature of the infectious agent: clearly this would be a tremendous breakthrough as would a means of positively identifying the infection in sub-clinical form. However, the difficulties of achieving this are acknowledged and the scrapie experience exemplifies the difficulties of making progress in this direction.

(vii) Genetic studies to determine whether there are any genetic factors involved in the disease expression in cattle.

(viii) The surveillance of humans at particular "risk" and formal monitoring of CJD cases, particularly in occupational groups exposed to bovine tissues.

8.5.3 The Working Party regards research as essential, for if there is any vertical or horizontal transmission the results will have a critical bearing on whether or not there is sufficient understanding of the disease to be able to control and eventually eliminate it. It will also have vital implications in terms of the ability or otherwise to maintain our important export trade in cattle, semen and embryos. And above all it may lead to complete reassurance about the lack of risk to human health or point the way to eliminating practices that could open up new pathways for infection.
9. GENERAL CONCLUSIONS

9.1 Bovine spongiform encephalopathy belongs to a group of diseases that are particularly intractable: the precise nature of the causative sub-viral agent is uncertain, their incubation periods are long, diagnosis is difficult except in the terminal stages and the mechanisms of transmission are variable and often obscure. One such disease, scrapie, has been widespread in sheep flocks in Britain and in other countries for at least two centuries, whilst CJD, a human encephalopathy with a worldwide distribution, has remained rare.

9.2 From present evidence, it is likely that cattle will prove to be a "dead-end host" for the disease agent and most unlikely that BSE will have any implications for human health. Nevertheless, if our assessments of these likelihoods are incorrect, the implications would be extremely serious. Thus, we greatly welcome the speed with which the Ministry of Agriculture, Fisheries and Food has brought forward regulations based on the veterinary evidence and on our recommendations and are encouraged by what we have learned of the positive response from the animal foods and farming industries to ensure the effectiveness of the regulations.

9.3 Assuming there is no vertical or horizontal transmission, the strict adherence to the regulations preventing the incorporation of infective material in calf and cattle feed should (after about 4 years) lead to a fall in the number of new cases and, on present evidence, after about 9 years the disease is likely to be extinct in Great Britain. In the meantime, farmers will have to exercise continual vigilance to ensure that animals exhibiting early symptoms are identified and prevented from entering the human food chain.

9.4 This problem has arisen as a result of the practice of feeding ruminant materials to herbivores, which are thus exposed to infective risks against which they have not evolved any defences. Such practices are a feature of modern intensive agriculture, but inevitably (as with BSE, and bacterial pathogens in poultry) they open up new pathways for infection to the farmed animals and potentially from them to man, via food and/or medicinal products. We note that animal meal supplements do increase the rate of growth of the animals, whilst also providing a superficially efficient way of disposing of animal waste. But we believe that the risks from inadequately sterilised animal products are such that this method of disposing animal waste should be changed so as to eliminate these novel pathways for pathogens. We urge Ministers to address this general problem as part of the adjustment of the framework of the agricultural policy of the EC in the coming years.
10. **SUMMARY**

10.1 We were asked to advise the Ministry of Agriculture, Fisheries and Food and the Department of Health on "the implications of Bovine Spongiform Encephalopathy and matters relating thereto" [1.1, 1.3].

10.2 We have concluded that bovine spongiform encephalopathy (BSE) is one of the transmissible encephalopathies caused by an unconventional infectious agent with a prolonged incubation period [3.1]. The epidemiological evidence suggests this new disease has appeared as a result of contamination of meat and bone meal derived partly from sheep offal and fed to British cattle from the early 1980's. Contamination had arisen because modern rendering practices failed to destroy the agent of scrapie, the endemic spongiform encephalopathy of sheep [4.2].

10.3 To prevent further infection in cattle the use of ruminant-based protein in ruminant rations has been banned [7.1]; we recommended that this ban be continued indefinitely [7.1.2].

10.4 Concerned at the remote chance that this new infection could be transmitted orally to man, we recommended the destruction of carcasses of cattle with suspected BSE [7.2] and prohibition of the use of milk from such cows for humans [7.3]. These recommendations have already been acted upon.

10.5 Considering other possible routes of transmission we have drawn the attention of the Licensing Authority to the potential of transfer of BSE agent in human and veterinary medicinal products [8.2]. We draw the attention of the Health and Safety Executive to possible exposure of various occupational groups to BSE agent [8.3]. We ask that specialist branches of the medical profession be alerted to the possible emergence of a new spongiform encephalopathy presenting as Creutzfeldt-Jakob disease [5.3.6].

10.6 Our deliberations have been limited by the paucity of the available evidence. Further research work in this area is essential. We recommend that the new Consultative Committee on Research coordinates investigations in this field [8.5.1] and we make suggestions for studies in the areas we consider to have special priority [8.5.2]. We stress the particular importance of continuation of a study of possible transmission in cattle [8.1].

10.7 We note that this disease appears to have originated from unnatural feeding practices as found in modern agriculture. We question the wisdom of methods which may expose susceptible species of animals to pathogens and ask for this general issue to be addressed [9.4].

R Southwood (Chairman)
M A Epstein
W B Martin
J Walton

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### FIGURE 2

<table>
<thead>
<tr>
<th>AGE (yrs)</th>
<th>1987*</th>
<th>1988*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. animals at risk</td>
<td>No. cases</td>
</tr>
<tr>
<td>2</td>
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<td>13</td>
</tr>
<tr>
<td>TOTAL</td>
<td>21910</td>
<td>270</td>
</tr>
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</table>

*based on: 188 herds in 1987
1181 herds in 1988

Age specific incidences of confirmed and clinically suspect cases during 1987 and 1988 within herds in which at least one case of BSE has been confirmed histopathologically.
FIGURE 3
INCIDENCE (%) OF DAIRY HERDS WITH CONFIRMED BSE
NOVEMBER 1986 TO DECEMBER 1988

Incidence %

- 0 to 0.09
- 0.1 to 1.99
- 2 to 3.99
- 4 to 5.99
- 6 to 9.99
- 10 to 18
### FIGURE 4

**INCIDENCE OF BBE AFFECTED DAIRY HERDS** (up to 31st Dec '83)

<table>
<thead>
<tr>
<th>COUNTY</th>
<th>NUMBER OF DAIRY HERDS AFFECTED</th>
<th>NUMBER OF DAIRY HERDS AT RISK</th>
<th>INCIDENCE % HERDS</th>
</tr>
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<tr>
<td><strong>REGION: SOUTH-EAST</strong></td>
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</tr>
<tr>
<td>BERKS</td>
<td>23</td>
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<td>BUCKS</td>
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<tr>
<td>HANTS</td>
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<td>I.O.W.</td>
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<td>136</td>
<td>5.9</td>
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<tr>
<td>KENT</td>
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<td>OXON</td>
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<td>SURREY</td>
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<td>200</td>
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<tr>
<td>E SUSSEX</td>
<td>19</td>
<td>368</td>
<td>5.6</td>
</tr>
<tr>
<td>W SUSSEX</td>
<td>45</td>
<td>332</td>
<td>13.6</td>
</tr>
</tbody>
</table>

| **REGION: SOUTH-WEST** | | | |
| AVON  | 17  | 671  | 2.5  |
| CORNWALL | 180 | 2175 | 8.3  |
| DEVON  | 242 | 353  | 6.8  |
| DORSET | 106 | 1167 | 9.1  |
| GLOS.  | 54  | 733  | 7.4  |
| SOMERSET| 108 | 2021 | 5.3  |
| WILTS  | 71  | 1025 | 6.9  |

| **REGION: NORTHERN** | | | |
| CLEVELAND | 1  | 99  | 1.0  |
| CUMBRIA   | 30 | 2639| 1.1  |
| DURHAM    | 3  | 401 | 0.8  |
| HUMBERSIDE| 5  | 268 | 1.9  |
| NORTHUMBERLAND | 5 | 228 | 2.2 |
| YORKS N   | 50 | 2456| 2.0  |
| YORKS S   | 2  | 251 | 0.8  |
| YORKS W   | 8  | 623 | 1.1  |

| **REGION: MID AND WEST** | | | |
| CHESHIRE  | 31 | 1884 | 1.7 |
| DERBYS    | 15 | 1323 | 1.1 |
| HEREFORD & WORCESTER | 33 | 908 | 3.6 |
| LANCs     | 35 | 1982 | 1.8 |
| LEICS     | 33 | 661  | 5.0 |
| MERSEYSIDE| 3  | 42   | 2.3 |
| Notts     | 6  | 237  | 2.5 |
| SALOP     | 40 | 1489 | 2.7 |
| STAFFS    | 30 | 1804 | 1.7 |
| W. MIDLANDS | 2 | 69  | 2.9 |
| WARWICKS  | 7  | 421  | 1.7 |

| **REGION: EASTERN** | | | |
| BEDS     | 5  | 72  | 6.9 |
| CAMBRIDGE| 8  | 73  | 11.0 |
| ESSEX    | 3  | 184 | 1.6 |
| HERTS    | 6  | 130 | 4.6 |
| LINCS    | 17 | 275 | 6.2 |
| NORFOLK  | 10 | 381 | 2.6 |
| NORTHERNS| 8  | 237 | 3.4 |
| SUFFOLK  | 21 | 253 | 8.3 |

| **REGION: WALES** | | | |
| 109 | 7178 | 1.5 |

| **REGION: SCOTLAND** | | | |
| 33 | 3462 | 0.9 |

| **OTHERS** | | |
| ISLE OF MAN | 3 | 450* | 0.7 |
| GUERNESEY | 15 | 87 | 17.2 |
| JERSEY | 0 | 110 | 0 |

* all cattle herds
Month/Year onset of clinical signs

762 cases, onset date unknown
27

* Incomplete data containing suspect cases not yet confirmed. There will also be many additional cases for these months which have not yet been diagnosed or suspected; the final total will be higher.

FIGURE S

YEAR OF ONSET DISTRIBUTION OF BSE CASES BY MONTH AND
12. REFERENCES


47. Royal Commission on Environmental Pollution. Agriculture and Pollution. Seventh Report (1979); Cmdn 7644 HMSO (280pp)


APPENDIX 1

RENDERING IN GREAT BRITAIN

1. Rendering is a cooking and separating process whereby animal waste is sterilised and fats and protein extracted. Up to 80% of the material for rendering comes from abattoirs and boning-out plants, around 10% from retailers such as butchers and 10% from knackers, restaurants, kennels etc. The end products of rendering are edible fats, which are derived from edible fat inputs and processed separately from non-edible material, and tallow and meat and bone meal derived from non-edible material. Greaves are an intermediate solid product which is further processed into meat and bone meal.

Tallows are used for soap manufacture, fat splitting and animal feeds and were the traditional main products of the rendering process. The nutritional value of meat and bone meal was realised in the early 1920's and in the post war years has been used in animal feeds stuffs.

2. In 1988 there were 41 rendering plants in Great Britain in operation producing tallow and greaves, and in many cases further processing the greaves to produce meat and bone meal. Through the helpful cooperation of the plant owners and the UK Renderers Association detailed information on these plants was obtained during 1988 by the State Veterinary Service. The following is a summary of these findings.

3. 1.3 million tonnes of raw material are processed by these plants each year. This material comprises 15.9 per cent fat, 30.5 per cent bones, 33.4 per cent offal, 8.9 per cent carcases and 11.5 per cent of other mixed material. The species composition of this material was estimated to be at 44.8 per cent bovine, 15.3 per cent ovine, 20.9 per cent porcine and 19.0 per cent of mixed origin including poultry.

The output of these plants in 1988 was 350,000 tonnes of meat and bone meal and 230,000 tonnes of tallow.

4. Batch rendering, the traditional method of cooking, is used by 28 plants involving some 26,000 tonnes of material per month. The mean particle size of material entering these cookers is 10 cm. Commonly each batch is heated for 1.5 to 2 hours to maximum temperatures ranging from 102 to 150°C under atmospheric pressure. In some plants the load is discharged once the maximum temperature is reached, in others there may be a holding time of up to 30 minutes.

5. Continuous rendering is used by the remaining 13 plants which process more than 70,000 tonnes of material per month. The first such plants were installed in the early 1970's. The mean particle size of material entering these cookers is 3cm.

a. Stork Duke Cookers
Temperatures of 135 to 145°C are achieved in the 5 cookers of this type. Independent studies have indicated that the residence time in these cookers is just over an hour.

*see Monopolies and Mergers Commission report (1986)
*Animal Waste: a report on the supply of animal waste in Great Britain* HMSO. Cmnd 9470.

32
b. Stord Bartz Driers
Temperatures of between 80 and 145°C are achieved in the 9 cookers of this type. Experiments at one plant indicated a minimum residence time of 60 minutes with an average of 2.5 hours. The exposure to maximum temperatures occurred two thirds of the way along the cooker giving an exposure to this temperature for about 35 minutes.

c. Carver Greenfield Systems
There are three plants of this type which heat material for 30 to 40 minutes to a maximum of 104 to 123°C and being at the maximum temperature for approximately 15 minutes. Recycling occurs in this process.

d. Protech System
Two new plants using this system have been commissioned recently. Minced raw material is heated to 95°C for 3 to 7 minutes. The solids are then dried in one plant in hot air which starts at 800 to 900°C and finishes at 110°C, and in the other in batch cookers at 120 to 130°C.

6. Comment from the Working Party

There is a lack of hard information on the time-temperature profiles in rendering plants under normal operating conditions, and no information on the usual extreme ranges that might be encountered. (The lowest temperatures for the shortest time are the most critical conditions). However, whereas any heat treatment might be expected to reduce the infectivity of scrapie agent somewhat, none of the current processes would appear capable of eliminating all strains of scrapie agent. Under unfavourable conditions, the time-temperatures might even not be adequate for all the more usual pathogenic organisms.
APPENDIX 2

EVIDENCE RECEIVED BY THE WORKING PARTY

20 June, 10 November, 16 December, 1988, 3 February 1989: oral and written evidence from Mr J. Wilesmith

1 September, 23 September, 17 October and 2 December: correspondence from Dr D Doyle, consultant neuropathologist concerning epidemiology of BSE and human spongiform encephalopathies, unusual cases of CJD, compensation for BSE and exposure to BSE during veterinary pathological examinations.

19 October 1988: prepublication draft sent by Dr H Fraser of the Neuropathogenesis Unit, Edinburgh.

27 October 1988: letter from Dr E Poole, EEG Department, The Radcliffe Infirmary, Oxford on how BSE might present in humans.

2 November 1988: report from the Chief Veterinary Officer of an investigation into rendering plants in Great Britain.

4 November 1988: report and draft publications from Dr J Hope of the Neuropathogenesis Unit, Edinburgh.

10 November: oral evidence from Dr R Kimberlin, formerly of the Neuropathogenesis Unit, Edinburgh.

1 December 1988: Report from Mr B Aldridge on published and pre-publication studies on BSE from the Royal (Dick) School of Veterinary Studies, Edinburgh.

2 December 1988: report from the Chief Medical Officer on CJD in human growth hormone recipients

13 December 1988: letter from Mr B Ahern, farmer in Taunton, concerning early cases in his herd.

2 January 1989: Prepublication report from Drs W.C. Foote (Utah State University) & J.R Pitcher (Texas) on scrapie in USA.

1 February 1989: Comments on specific issues by Dr J T Hughes, Department of Neuropathology, Radcliffe Infirmary, Oxford.

3 February 1989: Evidence from the Ministry of Agriculture, Fisheries and Food on the rendering industry.
APPENDIX 3
OFFICIAL CORRESPONDENCE FROM THE WORKING PARTY

21 June 1988: letter from Chairman to Mr D Andrews, Permanent Secretary (MAFF) with interim recommendations from first meeting of the working party.

14 November 1988: letter from chairman to Mr D Andrews (MAFF) with interim recommendations from second meeting of the working party.

14 November, 7 December and 23 December 1988: correspondence with Professor Asscher, chairman of CSM.

20 December 1988: letter from chairman to Mr Andrews (MAFF) about monitoring of offspring of cattle affected with BSE.

20 December 1988: letter to Dr T Little, Veterinary Products Committee.

16 August 1988: letter from secretariat to Dr J S Ashley, OPCS.

24 June and 15 November 1988: letters from secretariat to Dr D Gompertz, Health and Safety Executive.

APPENDIX 4

ABBREVIATIONS USED

BSE: Bovine spongiform encephalopathy
CJD: Creutzfeldt-Jakob disease
CSM: Committee on Safety of Medicines
EEG: Electro-encephalogram
MAFF: Ministry of Agriculture, Fisheries and Food
MRC: Medical Research Council
OPCS: Office of Population Censuses and Surveys
SAF: scrapie associated fibrils
TB: tuberculosis
TME: transmissible mink encephalopathy
VPC: Veterinary Products committee
DEPARTMENT OF HEALTH
MINISTRY OF AGRICULTURE, FISHERIES & FOOD

REPORT OF THE WORKING PARTY
ON BOVINE SPONGIFORM ENCEPHALOPATHY

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February 1989
Oxford
3rd February 1989

To The Secretary for State for Health, &
The Minister for Agriculture, Fisheries and Food,

As you know, in April 1988 I agreed to chair a Working Party which was to be set up to examine all aspects of the newly identified cattle disease called Bovine Spongiform Encephalopathy (BSE) and to advise accordingly.

Following the first meeting of the Working Party on 20 June 1988, I wrote to your Departments with two recommendations which we considered needed urgent attention. The first was that as a precautionary measure, at least until more is known about BSE, the carcases of affected animals should be destroyed. The second was that an expert Consultative Committee on Research should be established to advise on the research which is in hand and that which is required to answer questions identified by this Working Party. I am very pleased that the Government accepted and implemented both these recommendations, as described in the Report.

Three further recommendations were made following the second meeting on 10 November 1988. These were, firstly, that the ban on the use of ruminant-based protein in rations for ruminants should continue indefinitely. This recommendation was made because the Working Party could not be wholly sure that rendering as currently practised would eliminate the agents causing BSE. In addition, although the transmission of BSE via milk is very unlikely, we recommended that milk from suspect BSE cattle should be destroyed as a precautionary measure. Finally, we re- emphasised a point made in my earlier letter, namely, that it was vital to be able to "keep tabs" on offspring of affected animals in order that the question about maternal transmission can be answered.

Again I am pleased to be able to record the Government's positive response with the prohibition on the use of milk from suspect animals for human or animal consumption and an extension of the feed ban throughout 1989, together with a statement by the Minister that it will be necessary to continue the feed prohibition beyond the end of 1989 unless processing methods which are sufficient to destroy the agent have been identified and are widely available.

We have now had an opportunity to consider further various aspects of this new disease problem and accordingly make a number of recommendations. However, we wish to emphasise that in several areas the need for any further action will be dependent on the results of research into the disease. Furthermore, because of the nature of the disease, particularly its long incubation period, results cannot be expected for some time. In the circumstances the recommendations focus on the importance of this research. We have tried to identify the main areas of research which we regard as essential and those which should be considered by the newly established Consultative Committee on Research.
REPORT OF THE WORKING PARTY ON BOVINE Spongiform Encephalopathy

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1. INTRODUCTION

1.1 The establishment of the Working Party on Bovine Spongiform Encephalopathy (BSE)

In May 1988 a Working Party was established to examine the implications of Bovine Spongiform Encephalopathy (BSE), a newly identified neurological disorder of cattle, in relation to both animal health and any possible human health hazards and to advise the Government on any necessary measures.

1.2 Membership

The membership: Professor Sir Richard Southwood, PhD, DSc, F.I.Biol, FRS - Linacre Professor of Zoology, University of Oxford, (Chairman).

Professor M A Epstein, CBE, MD, DSc, PhD, FRCPath, FRCP, FRS - Emeritus Professor of Pathology, University of Bristol.

Dr W B Martin, PhD, DVSM, F.I.Biol, FRSE, MRCVS - formerly Director of the Moredun Research Institute in Edinburgh.

Sir John Walton, TD, MD, DSc, FRCP - Warden of Green College, Oxford; formerly Professor of Neurology, University of Newcastle upon Tyne.

Expert Adviser - Mr J Wilesmith, BVSc, MRCVS - Ministry of Agriculture, Fisheries and Food.

Joint Secretariat - Dr H Pickles, PhD, MRCP - Department of Health.

Mr A J Lawrence - Ministry of Agriculture, Fisheries and Food.

1.3 Terms of Reference

The terms of reference are "To advise on the implications of Bovine Spongiform Encephalopathy and matters relating thereto".

2. HISTORY OF BOVINE SPONGIFORM ENCEPHALOPATHY

2.1 The disease

Bovine Spongiform Encephalopathy (BSE) is a slowly progressive and ultimately fatal neurological disorder of adult cattle. It has been given this name because of the spongy appearance of brain tissue, known technically as grey matter vacuolation, when sections are examined under the microscope. BSE was first identified as an entity by the Ministry of Agriculture, Fisheries and Food's Central Veterinary Laboratory, Weybridge in November 1986 (51), although retrospective consideration of clinical records suggests that it may have occurred as early as April 1985. All the available evidence suggests that BSE belongs to a group of progressive, degenerative diseases of
the central nervous system, which invariably prove fatal. They are caused by a group of unconventional transmissible agents. The other similar diseases include scrapie in sheep and goats, transmissible mink encephalopathy and Creutzfeldt-Jakob Disease (CJD) in humans (43,10,6) [see Section 3].

2.2 Clinical signs

The clinical signs involve behavioural, gait and postural abnormalities and usually begin with evidence of apprehension, anxiety and fear. Some animals may paw the ground or continually lick their nose. There is increased reaction to sound and touch. A swaying gait, sometimes coupled with high stepping of the feet, is most evident in the hind limbs. Signs may progress from reduced milk yield, weakness and loss of condition, to frenzy and aggression. Kicking and general nervousness in the milking parlour are frequently reported signs. The gait abnormalities can be seen on grassland, especially when urged to move at the trot. On concrete, difficulty in turning may be accompanied by slipping and falling. In the advanced stages animals become recumbent (51,48,52).

2.3 Duration of illness and age of affected animals

Following the onset of clinical signs, the condition of the animal deteriorates until it either dies or becomes unmanageable and has to be destroyed. This usually takes anything from 2 weeks to 6 months as illustrated at Figure 1. Since the advent of compulsory notification and slaughter, the average time between notification and slaughter has been 8 days, with over 80% slaughtered within 3 weeks. All the cases of BSE have occurred in adult animals, with an age range of 3 to 11 years. However, most cases have occurred in animals between 3 and 5 years of age as shown in Figure 2. There is evidence that if the animal is stressed, e.g. on separation from the herd or on being sent to market, the development of clinical signs accelerates (G Wells & J Wilesmith, personal communication).

2.4 Diagnosis

Observations on suspect cases of BSE over a period of time have provided a sound basis for clinical diagnosis. Preliminary studies in relation to the use of electro-encephalograms (EEG) as an ancillary aid to diagnosis have shown that the EEGs in two cases of BSE differed markedly from those seen in similarly aged clinically normal cattle and those recorded from cases of other types of experimental neurological disease in other ruminants (1). The EEG abnormalities also show a striking similarity to those which are usually found in human CJD. Confirmation of disease is however only possible following post-mortem histological examination of brain tissue. The unconventional agent which is thought to cause BSE is quite unlike any bacteria or known viruses. Its structure and manner of replication does not provoke any detectable antibody response in the host. Because of this there is at present no blood or other tissue test available for detecting the disease in the live animal.

2.5 Incidence and distribution of the disease in Great Britain

2.5.1 In the period from November 1986, when the disease was first identified as a separate entity, to 31 December 1988 there were 2160 confirmed cases on 1667 farms. The current incidence is estimated to be in the region of 350-400 confirmed cases a month. This represents an annual incidence of around 1 case per 1000 in adult cattle in Great Britain where the total population of adult cattle is 4 million. As indicated in paragraph [7.2.3] it is considered that this provides an accurate picture
of the incidence of the disease in Great Britain. A feature of the disease so far has been that in the majority of affected herds only a single animal has developed the symptoms (52). Although cases of BSE have occurred in most parts of Great Britain there has been a much higher concentration in the southern half of England. An illustration of the geographical distribution of the incidence and number of dairy herds with confirmed cases up to 31 December 1988 by region and county is shown in Figures 3 and 4.

2.5.2 BSE was made a notifiable disease on 21 June 1988. From that date it became a legal requirement to report suspect cases. Before then most reports of suspect disease were made by private veterinarians to the Ministry of Agriculture, Fisheries and Food's Veterinary Investigation Centres. Up to 21 June 1988 867 cases of disease were confirmed. From then up to 31 December 1988 974 cases were confirmed. The number of cases confirmed by month and year is shown at Figure 5.

2.6 Incidence of disease elsewhere

BSE has not been reported outside the British Isles but two research workers have reported that they suspected the presence of a scrapie-like disease of cattle in the USA (36). However, the combination of critical factors which has probably led to the emergence of the disease in this country [see section 4.2] may not exist in many other countries, if anywhere. These factors include the existence of a sheep population in which scrapie occurs and a feed and cattle industry which produces and uses ruminant-derived meat and bone meal in calf rations.

3. TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

3.1 The causative agents

There are a number of transmissible spongiform encephalopathies affecting animals and man which are caused by unconventional infectious agents (43,6). The agents responsible have not been completely characterised, although their composition appears to be very similar, with a peptide as a major component. There are three conflicting interpretations of existing knowledge (25), the agent being termed either a prion, a virino, or a filamentous virus and defined as follows:-

i. "a prion is a small infectious pathogen containing protein (PrP); it is resistant to procedures that modify or hydrolyze nucleic acids." (42).

ii. "a virino is an infectious pathogen containing a core of nontranslated nucleic acid associated with cellular proteins" (30).

iii. a filamentous virus; it being argued that scrapie agent's resistance to inactivation is limited to small subpopulations and is not unlike that of conventional viruses (45).

These small infectious agents have also been termed "slow viruses", "unconventional agents" and "subviral pathogens". They are unusually resistant to heat and to the normal sterilisation processes (31) [see para 3.9 below].
3.2 Animal spongiform encephalopathies

The most widely recognised spongiform encephalopathy of animals is scrapie, which is a fatal progressive neurological disorder of sheep. Scrapie has been reported from many countries of the world and has been recognised in British sheep flocks for over two centuries, having been first recorded in 1732. It affects sheep and goats naturally and can be transmitted experimentally to several animal species, particularly mice, after which the disease may be passaged in that species with a significantly reduced incubation period. There are a few records of similar encephalopathies arising naturally in animals such as a transmissible encephalopathy in mink (*Mustela vision*) (26), chronic wasting disease in captive mule deer (*Odocoileus hemionus*) and a spongiform encephalopathy in a sub-species of the red deer, the Rocky Mountain elk (*Cervus elaphus sibiricus nelsoni*) in captivity (53,54). None of these diseases has been reported in similar species, captive or wild, in this country. Transmissible mink encephalopathy (TME) is believed to have arisen as a result of feeding raw sheep offal to ranched mink.

Transmission of the scrapie agent occurs naturally between sheep. Both maternal and lateral transmission is recognised (14) though the precise mode of transmission is not known (29) [see para 5.1.2]. Clinical disease does not generally appear until sheep are between 2.5 and 4.5 years of age. Affected sheep show behavioural changes such as intense itching (hence the name scrapie) and incoordination which progresses to an inability to stand and eventually death. Antibodies to the scrapie agent have never been detected and no test which will confirm the presence of disease during life has ever been discovered.

Brain changes are predominantly degenerative, the main feature being cell vacuolation. There is neuronal loss and gliosis. Another feature of scrapie, and all spongiform encephalopathies, is that inflammatory reaction is minimal or absent. In addition, abnormal fibrils, "scrapie associated fibrils" (SAF), can be detected in infected brain extracts with the electron microscope (39). The presence of these fibrils is now recognised as one identifying feature of the spongiform encephalopathies. Molecular studies of the fibrils from the brains of cattle affected with BSE have shown that they contain the same type of glycoprotein as is present in SAF (28). The pathological changes in hound ataxia and feline dysautonomia are quite different from those of the spongiform encephalopathies.

Strain variations of the scrapie agent have been recognised from mouse studies on the basis of pathological and biological properties (12). An unusual feature of the agent is its remarkable resistance to inactivation by a wide range of physical and chemical treatments such as ultra-violet light and formalin (23,16) [see para 3.9]. Although scrapie is caused by an infectious agent the expression of the disease depends on host genetic factors (15).

3.3 Human spongiform encephalopathies

Kuru, Creutzfeldt-Jakob Disease (CJD) and its even rarer variant, the Gerstmann-Sträussler-Scheinker (GSS) disease, are spongiform encephalopathies described in man. Like the animal disorders, they are progressive and universally fatal. Kuru is a spongiform encephalopathy that at one time was common in certain tribes in New Guinea, although not recognised elsewhere. Transfer of infection by the subviral pathogen was thought to occur through ceremonial handling and ingestion of human brains affected by the disease (21). As the disease is not vertically transmitted, the incidence of Kuru has decreased dramatically since these practices ceased around 1956, although several cases still occur each year in patients over 30 years of age; this is
consistent with an incubation period of 30 years or more (2).

3.4 Although a rare disease, occurring at an incidence of around 0.5 to 1.0 case per million per annum, CJD has been the subject of extensive study and the possibility of a relationship with scrapie explored. A small number of cases can be attributed to iatrogenic transmission from other cases of CJD through the transplantation of nervous tissue and corneas, and the use of brain electrodes and human growth hormone (44). In the majority of cases of CJD, the source of infection cannot be determined. Familiar cases are a small minority (generally under 10% \( ^1 \)) and there is a little support for direct case-to-case transmission. The epidemiology suggests that CJD is a disorder of minimal infectivity with an as yet undetermined route of transmission and a long incubation period: current evidence, from the small number of cases that have followed growth hormone treatment, is of periods up to 20 years. This group of cases also suggests that symptomless persons may exhibit pathological features in the brain tissues. The much more common dementia, Alzheimer’s disease, is not considered one of the spongiform encephalopathies, for although there are several overlapping properties (33,34), it is not generally regarded as transmissible.

3.5 Investigation of possible association between animal and human spongiform encephalopathies

Over the years, various studies have been conducted in order to explore the possibility that scrapie in sheep might be a source of CJD in humans (4,24,11,7). These include studies designed to examine tentative associations between sheep and CJD. In one of the most recent studies (7), a total of 329 patients was identified in France between 1968-1982 as having died of CJD. On the link with scrapie, the authors wrote:-

"Conflicting evidence has been accumulated in our study about the possibility that scrapie in sheep might be a source of CJD in humans. Although two of the patients in this series were shepherds, no case of CJD occurred in any other occupational group in direct contact with sheep carcases or products. The regional distribution of CJD was unrelated to the location of scrapie-infected flocks of sheep, or to the commercial destinations of lamb from areas in which scrapie was endemic. In one endemic area, we were unable to isolate scrapie virus from either brain or visceral tissue taken from lambs and ewes selected at random in a centrally located slaughter house. The high incidence of CJD found in Algerian and Tunisian immigrants could have been either genetically determined, or the result of early environmental viral contamination, including youthful exposure to the heavily sheep-oriented North African cuisine" (7).

3.6 In studies of the worldwide incidence of CJD, associations with eating sheep brain or eyeballs have been described (4,11), but transmission by the oral route from sheep is not supported by other evidence, including a case control study in Libyan Jews (24). There are obvious difficulties in relating a disease with a very long incubation period to dietetic habits. CJD occurs at its usual frequency in Japan where scrapie is very rare and Australia where it has never been recorded; CJD has also been reported in a lifelong vegetarian (7).

3.7 Scrapie has been endemic in Great Britain for centuries without there being any evidence to show an incidence of CJD higher than the international average in the human population (37).
3.8 Transmission of BSE to mice

Mice inoculated with brain homogenates from two separate BSE cases have, after 10-11 months, shown signs of an encephalopathy (20). The histopathological changes observed are indistinguishable from those produced in mice following primary transmission of sheep scrapie. Four different strains of mice were used; signs so far have been seen in two strains (RIII,C57) with the observed difference in the median incubation period in these two strains being 80 days. Studies are in progress to determine whether this difference in expression in the strains of mice can be accounted for by differences in the doses administered or whether, as with scrapie, sensitivity to the expression of the disease varies with the host genotype.

3.9 Destruction of agents of spongiform encephalopathies

The agents responsible for the spongiform encephalopathies show unusual resistance to the processes that are usually used to inactivate infectious organisms such as wet and dry heat, ultra-violet and ionising radiation (3), alkylating agents, organic solvents, concentrated salt solutions and many detergents (23,16). Although any exposure to temperatures over 100°C will lead to some loss of infectivity (46), in various experiments complete loss of the infectious agent was not achieved by heat at 121°C for 1 hour (scrapie) or 240°C for 1 minute (scrapie and CJD) (8) or 126°C for 1 to 2 hours (scrapie) (31). Some strains of agent (e.g. 22A scrapie) are more heat-resistant than others. The current recommendations for sterilisation procedures for infected equipment contaminated by patients with CJD is, for the autoclaving of a porous load, a single cycle at 134-138°C (30 lbs psi) for 18 minutes hold time or six separate cycles at 134-138°C for 3 minutes hold time each.* Formalin fixation appears to increase heat-resistance of scrapie agent (50) and the current recommendations may be inadequate under these circumstances.

Scrapie and CJD agents have also been shown to be resistant to various chemical disinfectants, although higher concentrations (at least 2% available chlorine) of sodium hypochlorite may be effective in at least reducing the titre if contact is maintained for 30 minutes or more (31) as may immersion in 1.0 N sodium hydroxide for 1 hour at room temperature (8).

3.10 In summary, the present state of knowledge shows that all these diseases have similar pathologies with spongiform change in the central nervous system and with abnormal fibrils identified ultrastructurally; they also produce similar EEG abnormalities; they are inevitably fatal and the causal subviral agents are not destroyed by normal sterilisation processes. The period from infection to the expression of signs is long (in relation to the life span of the animal), e.g. from ten to eleven months for BSE in mice to as much as 30 years for Kuru in humans. The agents may be transmitted by direct injection into the nervous system, by transplantation of tissues or, in humans, injection of hormone derived from human sources; some transmission is almost certainly oral (Kuru, scrapie to cattle giving BSE, and scrapie to mink giving TME), but the usual mode of transmission of the most widespread disorders (scrapie and CJD) is unclear. Expression of these disorders may also be influenced by host genotype.

*DA(84)16 DHSS circular "Management of Patients with Spongiform Encephalopathy (CJD)"
4. THE CAUSE OF BOVINE SPONGIFORM ENCEPHALOPATHY: THE EPIDEMIOLOGICAL EVIDENCE

4.1 Methods

4.1.1 The Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food has been undertaking an epidemiological study to determine the cause of the disease (52). A comprehensive questionnaire is being used to obtain epidemiological data about herds which have had one or more confirmed cases. The information obtained includes the date of birth, breed, sex, herd of origin (if purchased), breed society herd book number and pedigree records (where appropriate), date of clinical onset and stage of pregnancy at onset, the identities of offspring and the presence or otherwise of specific clinical signs. Specific descriptions of the presenting signs and progression of the disease are also obtained from the herdsmen and veterinary surgeons.

4.1.2 In addition, information has been obtained in relation to the herd type, size and age structure, whether or not there have been sheep on the farm since 1980, the destination of animals sold and the origin of breeding animals since the birth of the initial case, and details of the use of pharmaceutical products, vaccines, pesticides and herbicides. Feeding practices since the birth of the initial case are also determined.

4.1.3 A computer simulation model has been constructed on the hypothesis that BSE is caused by an unconventional transmissible agent. It was designed to examine the time of onset and duration of exposure, the incubation period, distribution and age classes of animals exposed. The model consists of a large population of calves, young stock and adult stock. The latter have been subjected to a specific culling rate obtained from previous studies of dairy herds. Values for the exposure parameters and incubation period have been imposed on the model. The incubation period is assumed to have a log normal distribution, and to exhibit no variation with age at first exposure. The age specific incidences of BSE in herds with confirmed cases are used to assess the validity of the exposure and the incubation period parameter. The simulation is also used to predict changes in age specific incidences in future years (see para 4.2.7).

4.1.4 The complete herd breeding records obtained from one multiple case herd have been analysed to examine the hypothesis that BSE is the result of an autosomal mode of inheritance. For this, the pedigrees of all confirmed cases in Great Britain, accumulated to the end of 1988, have been used to produce a list of putative heterozygous carrier bulls, i.e. the sires or maternal grandsires of confirmed cases. This provides for the identification of animals from the specified herd whose sire and maternal grandsire were putative heterozygous carriers (52).

4.2 Results and Conclusions

4.2.1 The epidemiological picture, as shown by the distribution of cases by month and year of onset, is shown in Figure 5. It is typical of an extended common source epidemic. Movement of cattle between known affected herds does not account for the occurrence of cases and the initial cases in different herds developed clinical signs within a relatively short period of each other. All affected animals therefore appear to be index cases. No evidence of cattle-to-cattle transmission has yet been observed. The age of the confirmed cases ranges from 3 to 11 years and their year of birth from
1979 to 1984. BSE had been confirmed in 4 bulls by the end of December 1988. The incidence of affected dairy herds increases directly with the herd size: 75% of herds have only experienced single cases. The high incidence of affected herds in the South of England suggests that there is a true regional variation in risk.

4.2.2 Cases have been studied in detail to seek a common factor in terms of treatments given to calves, young stock or the adult herd. The use of organophosphorus fly sprays, systemic pyrethroid sprays, synthetic pyrethroid ear tags (for fly control) and organo-phosphorus warblecide have not been shown to be a common factor. Newly introduced vaccines such as those for leptospirosis have been used only in a very small proportion of herds. There is therefore no evidence for the introduction of a novel infectious agent through a particular biological product. Similarly, other pharmaceutical products that have been introduced relatively recently eg anthelmintics and "reproductive hormones" and the use of weedkillers/herbicides and pesticides are not common factors. The absence of any association at the time of onset of clinical signs with either month or state of pregnancy/lactation was not consistent with an acute toxic effect of pharmaceutical products or agricultural chemicals, the use of which is usually restricted to particular months or seasons or to specific times in an animal's lifespan or reproduction cycle. Genetic studies have revealed that while some familial relationships between affected cattle in a small number of herds have been found, there is positive epidemiological evidence that excludes BSE from being exclusively a simply inherited disease. There is also no evidence that BSE has been introduced by imported cattle or semen. Finally, the transmission of the scrapie agent from sheep to cattle via direct or indirect contact on the affected farms appears to be an untenable hypothesis in view of the absence of sheep on 20% of the farms concerned.

4.2.3 The only common feature in all the cases that have been investigated is the use of commercial concentrates, either as finished rations, such as pelleted calf feed and dairy calf cake, or protein supplements used in home mixed rations. This points to meat and bone meal as being the vehicle of infection. Studies are continuing in order to try to determine more precisely the exposure of the affected and unaffected animals to meat and bone meal in commercial concentrates*. Meat and bone meal is distributed, and incorporated into animal rations, within a relatively small radius of its production, compared with tallow. The geographical variation in incidence indicates a geographical variation in risk which is not consistent with the distribution and use of tallow. In addition, in the rendering process the BSE agent would probably partition with the cellular residues of the meat and bone meal fraction, rather than with the lipids of tallow. The feed-borne hypothesis is also supported by the considerably greater incidence in dairy herds compared with beef suckler herds as there is a reduced rate of concentrate feeding, particularly with calves, in the latter herd type. 3.6% of dairy herds have been affected, whereas only 0.12% of beef suckler herds*. The positive association between herd size and the risk of occurrence of a case of BSE is likely to be due to an increase in the probability of purchasing an infected batch of food with increasing herd size.

* There are a number of formulations of proprietary concentrate rations for cattle. Concentrate rations for calves are produced in pelleted form and referred to as pellets, pellets or nuts and in a non-pelleted form referred to as a coarse mix. Pelleted concentrates for adult cows, particularly dairy cows, are the commonest formulation fed and these are referred to as cake, nuts or merely concentrates.

1600 out of 44782 dairy herds and 67 out of 54266 beef suckler herds up to 31 Dec 1988. There are around 1.9m adult beef cows and 2.1m adult dairy cows in Great Britain.
4.2.4 The occurrence of TME in ranch-reared mink, first recorded 40 years ago, seems to be a precedent for the food-borne transmission of the agent. The source of the infection in ranched mink in the USA was attributed to the feeding of scrapie-infected sheep or goat tissues (35). It is also interesting to note the occurrence, in a wildlife park in the UK, of a spongiform encephalopathy in a nyala (Tragelaphus angasi)* in June 1986 and a gemsbok (Oryx gazella)* in July 1987. These animals had no contact with each other and no source of a transmissible agent was evident at the time these cases were investigated. However, from March 1986 to March 1987, they were fed a commercial concentrate which included meat and bone meal. This ingredient was believed not to have been incorporated into the feed for 11 years prior to March 1986. If this is correct, then the disease presented in these species surprisingly rapidly.

4.2.5 The reason for the geographical variation in BSE incidence has not been firmly established, but studies are continuing. It cannot be explained simply by the geographical variation in dairy herd size distribution. One hypothesis is that it mirrors the geographical variation in the market share of cattle feedstuffs between the major compounders assuming that there is a variation between companies in the use and inclusion rate of meat and bone meal. There is some evidence that this explains the apparently anomalous difference in incidence between Guernsey and Jersey.

4.2.6 In every case of BSE investigated so far, animal protein had been fed to the animal. Herds that are present free of the disease have also been investigated and most of these have been fed rations containing animal protein. However a small number of herds (under 3%) has been identified where this has not occurred and none of these animals has developed the disease. This study is continuing.

4.2.7 The use of a computer based simulation model indicates that the values of the age specific incidences which have been observed are consistent with the following features. Firstly, both calves and adults (over 2 years of age) were exposed, but the risk of clinical disease was 30 times greater for calves than for adults. Secondly, an incubation period occurred with a range from 2.5 years to at least 8 years and a log normal distribution. The maximum incubation period that could have been observed in 1987 was 6 years (52). Thirdly, exposure of the cattle population commenced in the winter of 1981/82 and continued until at least the end of 1985. Further epidemiological data are needed to demonstrate that exposure and infection continued beyond 1985, but it seems likely that this was so until July 1988 [see 6.1].

4.2.8 There is no clear or single explanation why it appears that in 1981/82 cattle apparently first became exposed to an agent sufficient to result in clinical disease. On the other hand a number of factors have been identified which, combined, could be important in the occurrence of this epidemiological phenomenon. These include a significant increase in the sheep population in Great Britain which commenced in 1980 and has continued since; a possible increase in the prevalence of scrapie infected flocks; the greater inclusion of sheep heads in material for rendering; the greater inclusion of casualty and condemned sheep in material for rendering as a result of the reduction in the number of knackers' yards; the introduction of continuous rendering processes during the 1970s and 1980s, which may have resulted in the rendering of animal material at a lower temperature and/or for less time than previously [see appendix 1], and the decline in the practice of using hydro–carbon solvents for fat extraction since the mid-1970s. These factors provide a possible explanation for a change in exposure of cattle to ovine-derived protein and thus the scrapie agent (52,40,5).

* African antelopes
4.2.9 A further hypothesis to explain the occurrence of BSE is the emergence or selection of a strain or strains of the scrapie agent pathogenic for cattle. Mutations of the scrapie agent, which can occur after a single passage in mice, have been well documented (9). This phenomenon cannot be dismissed for BSE, but given the form of the epidemic and the geographically widespread occurrence of BSE, such a hypothesis would require the emergence of a mutant scrapie strain simultaneously in a large number of sheep flocks, or cattle, throughout the country. Also, if it resulted from a localized chance transmission of the scrapie strain from sheep to cattle giving rise to a mutant, a different pattern of disease would have been expected: its range would have increased with time. Thus the evidence from Britain is against the disease being due to a new strain of the agent, but we note that in the United States from 1984 to 1988 outbreaks of scrapie in sheep flocks are reported to have increased markedly, now being nearly 3 times as high as during any previous period (18). From enquiries we have made, it seems unlikely that any bone meal for cattle food has been imported into Britain from the USA.

5. THE TRANSMISSION OF BOVINE SPONGIFORM ENCEPHALOPATHY

5.1 In cattle

5.1.1 The epidemiological studies carried out so far have not revealed any evidence of vertical (dam to offspring) or horizontal (bovine to bovine) transmission of disease. Neither is there any evidence of transmission via semen or embryos. Over 300 offspring of cows in which BSE has been confirmed, together with the same number of control animals, are being monitored by the Ministry of Agriculture, Fisheries and Food's Central Veterinary Laboratory [see para 8.1]. The Laboratory is also undertaking research projects into the possible means of transmission. The occurrence and incidence of maternal transmission, should it occur, will probably not be evident from the field epidemiological study until after 1990.

5.1.2 Field observations and experimental work have established that there is transmission of scrapie from the infected ewe to the lamb. Various experiments have been carried out involving the transfer of fertilised embryos from scrapie-infected ewes to scrapie-free ewes and vice versa. From these and other studies it is concluded that the scrapie agent is not present in semen, in the very young embryo or the lamb at the time of birth (19,18). The placenta is highly infectious (41) and is the most likely source of infection for the new born lambs. Although the disease in goats behaves in a similar way to that in sheep, some species, such as rodents and mink which are susceptible to scrapie, act as dead-end hosts with no direct animal to animal transmission. At the present stage of knowledge it is impossible to predict whether cattle to cattle transmission of BSE will occur.

5.2 To other non-human animals

5.2.1 The concept of a "species barrier" in relation to scrapie has been the subject of discussion because of the variation in the success rate of primary transmissions of sheep scrapie to other species. Two reasons, apart from variation in the doses of agent administered, have been suggested. These are firstly that the strain of agent is unable to reach replication sites in the new host either because of its essential structure or because of some phenomenon involving donor tissues with which it happens to be associated. The second is that the agent in question fails to replicate even though it can reach sites in the recipient at which other strains of the agent
replicate. Even if these reasons do not apply it may be that replication of the agent is so slow, or the initiation of replication is so delayed, that disease does not occur during the new host's lifespan (21).

5.2.2 As mentioned above in 4.2.4, signs identical to those of a spongiform encephalopathy have already been described in two antelopes both of whom were fed meat and bone meal-containing rations. BSE has also been transmitted experimentally by intracerebral inoculation into mice (20). In theory other animals may have been exposed to the BSE agent, and there is a risk that this might occur in the future. Concern here arises not only for the health of the animals concerned, but in case other species might act as sources of yet further spread.

5.2.3 Since no natural infections have ever been described in non-mammalian species it seems unlikely that they would be susceptible to BSE, scrapie or any other spongiform encephalopathy. It may be noted, though, that poultry feed frequently contains both bovine and sheep tissues. Without specific tests for the agents concerned, it cannot be proven that poultry are unable to carry the agent in an infectious form, but it is considered that the chance of this is so small, and the risk were this to occur so remote, that no action is appropriate at this stage. However, if a specific test were to be developed, research on the agents of spongiform encephalopathies in non-mammals, including poultry, should be undertaken.

5.2.4 Other mammals exposed to sheep and bovine material include domestic pets and mink. Encephalopathy in mink is likely to present as TME but to date there have been no cases in the small UK mink population. There are no descriptions of naturally occurring spongiform encephalopathies in domestic pets such as cats and dogs. Even in the absence of any natural disease, domestic pets could well be susceptible to BSE were the agent to reach them in an adequate dose by an appropriate route. Whilst pet food frequently contains offal from both sheep and cows, so that the source material must have contained scrapie and possibly BSE agents, there is no evidence of relevant neurological disease in cats or dogs. It seems unlikely, but possible, that preclinical infection exists but is not revealed because of an incubation period longer than the natural lifespan. On the other hand, it may be that infection cannot be acquired orally by these species or that the high temperatures used in pet food canning destroys any infectious agent (see para 3.9). Nevertheless, transmission experiments in cats and dogs and surveillance of the health of domestic pets are items that should be brought to the attention of the Consultative Committee on Research and the veterinary profession. Hounds that are often fed uncooked carcasses would be particularly appropriate for study. Other ruminants, principally various deer and antelopes, would clearly be at considerable risk of developing this disorder if, contrary to current regulations, fed material with bone meal and meat residues from sheep or cattle.

5.3 Possible Transmission to Man

5.3.1 Kuru and Creutzfeldt-Jakob Disease demonstrate that humans are susceptible to spongiform encephalopathies. The potential routes of transmission of BSE from cattle to humans have been examined closely. With the very long incubation period of spongiform encephalopathies in humans, it may be a decade or more before complete reassurance can be given.

5.3.2 Information from several spongiform encephalopathies suggests that parenteral inoculation is much more efficient in transmitting disease than oral or topical exposure and that neural, and to a lesser extent, lymphoid tissue carry the infection whilst the risk is far less with other tissues. The theoretical routes of
transmission from cattle to humans can be presented in "risk" order to help clarify whether action is appropriate or research worthwhile.

5.3.3 The greatest risk, in theory, would be from parenteral injection of material derived from bovine brain or lymphoid tissue. Medicinal products for injection or surgical implantation which are prepared from bovine tissues, or which utilise bovine serum albumin or similar agents in their manufacture, might also be capable of transmitting infectious agents. All medicinal products are licensed under the Medicines Act by the Licensing Authority following guidance, for example from the Committee on Safety of Medicine (CSM), the Committee on Dental and Surgical Materials (CSDM) and their sub-committees. The Licensing Authority have been alerted to potential concern about BSE in medicinal products and will ensure that scrutiny of source materials and manufacturing processes now takes account of BSE agent.

5.3.4 Direct inoculation of bovine tissue could also occur accidentally in certain occupations, such as slaughtermen, veterinarians and laboratory workers. Guidance on safe working practices in general are drawn up by the Health and Safety Executive who have been alerted to the potential concern about BSE and in particular to the possible infectivity of placenta. No specific additional guidance on BSE is thought appropriate at this time. However adherence to recommended procedures in handling animals and animal products is clearly very important.

5.3.5 In these, as in other circumstances, the risk of transmission of BSE to humans appears remote. Nevertheless, because the possibility that BSE could be transmitted orally cannot be entirely ruled out, known affected cattle should not enter the human food chain and action now undertaken ensures this. What evidence there is does not suggest that milk can transmit any of the spongiform encephalopathies. Nevertheless, to be consistent with the earlier recommendation that cattle known to be infected with BSE should not be offered for human consumption, we have recommended that milk from cows suspected as having BSE should be destroyed. Action has also been taken here. Finally if the BSE agent were to be present in an animal it is most likely to be in the spleen and lymphatic tissues in the early stages of infection, and as the disease progresses in the brain and neural tissue (17,13,32). It has been suggested, although clinically affected cattle are being slaughtered and destroyed, that consideration should be given to products containing brain and spleen being so labelled, to enable the consumer to make an informed choice (27). The Working Party believes that risks as at present perceived would not justify this measure. We note that current regulations that require contents of processed food to be listed permit the generic terms "meat" and "offal". We consider that manufacturers of baby foods should avoid the use of ruminant offal and thymus; the latter can currently be described on food labels as meat.

5.3.6 It is a reasonable assumption that were BSE to be transmitted to humans, the clinical disorder would closely resemble CJD. Depending on the route of transmission, the incubation period could be as little as a year (as with some iatrogenic CJD cases) or several decades (as estimated for many natural CJD cases). Identification of any such cases as unusual or atypical would not be easy. However the Chief Medical Officer could consider whether specialist branches of the medical profession such as neurologists, neuropathologists and neurophysiologists, to whom cases of suspected CJD are referred for diagnosis, should be made aware of the emergence of BSE so that they can report any atypical cases or changing patterns in the incidence

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The Food Labelling Regulations 1984 (SI 1984 no 1306) and
The Meat Products and Spreaderable Fish Products Regulations 1984
(SI 1984 no 1506)
of disease. CJD also remains of considerable interest to epidemiologists and they should also be advised to watch for any changing patterns in relation to the disease. The Office of Population Censuses and Surveys is already reviewing deaths attributed to CJD and will be looking for any trends or particular occupational or other characteristics in the deaths certificated to CJD. The questions of specific monitoring of population groups considered at enhanced risk of BSE exposure, or more detailed surveys of CJD cases, are included amongst those to be referred to the Consultative Committee on Research.

6. THE FUTURE COURSE OF THE DISEASE

6.1 Estimate of number of future cases

As indicated above in 5.1.1 there is no evidence of maternal or horizontal transmission of BSE. If these methods of transmission are assumed not to occur it is possible to make an estimate of the order of magnitude of future incidence. The results of the epidemiological study so far indicate that exposure was not for a discrete short period, but from 1981/82 until at least 1985 and assumed from then until 18 July 1988 when legislation was introduced to prohibit the inclusion of ruminant-derived protein in ruminant feedstuffs [see paragraph 7.1.1]. There are however three factors which may have affected the exposure of cattle to the BSE agent since 1985. First, the introduction of milk quotas in 1984 resulted in lower rates of concentrate feeding to dairy cows and therefore a reduced exposure for adult animals; this is unlikely to have a significant effect as the majority of animals have been infected as calves. Secondly, as a result of the continuing increase in the sheep population, the proportion of ovine material entering rendering plants will have increased. Thirdly, the inclusion of infected cattle into the cattle food chain until 18 July 1988 could have increased the exposure. The effects of the latter two factors are impossible to quantify, but could be minimal and undetectable, resulting in essentially a constant exposure. If this is the case, and given the incubation period distribution, then a constant number of cases, of the order of 350-400 per month, can be expected; this is an incidence of 1 case per 1,000 adult cows per year. If the age structure of the national adult herd remains constant, as the usual life span of a milk cow in Great Britain is at present 5 to 6 years this rate of presentation of the disease will continue until 1993, a cumulative total of about 17000-20000 cases from cows currently alive and subclinically infected. Thereafter, if cattle to cattle transmission does not occur then a reduction in incidence would follow with a very low incidence in 1996 and the subsequent disappearance of the disease.

6.2 Estimated new infections in cattle

The estimates in 6.1 assume that no new infections have arisen or will arise after 18 July 1988 when the ban on ruminant protein in feed became operative; this ban is to continue unless processing in rendering plants is shown to be adequate to inactivate scrapie agent [see 7.1.2]. No allowance has been made for new infections arising from lateral transmission in cattle; there is no evidence from the available epidemiology that this has taken place [5.1.1] and evidence from other spongiform encephalopathies suggests it will be unlikely. No allowance has been made either for new infections arising from maternal transmission: insufficient time has elapsed to determine whether maternal transmission occurs in BSE and if so at what incidence. Given the age distribution of the BSE cases at the onset of clinical signs and therefore the number of offspring which will survive the minimum incubation period, the occurrence of maternal transmission, should it occur, is unlikely to be witnessed.
until 1990.

Though maternal transmission would increase the number of cases on its own it would probably be insufficient to sustain BSE in the national cattle population because it is likely that the number of offspring per case which will reach a susceptible age and produce their own offspring will be less than one. If transmission does occur this is most likely to be from the placenta and membranes, as in scrapie [para 5.1.2]. Environmental contamination from this source may be more readily controlled in cattle herds than in sheep flocks because of the differences in management, and we suggest that in those herds where the disease has occurred attention should be given to the rapid collection and destruction of placentae.

6.3 Estimate of BSE in other species

As mentioned in 4.2.4, BSE has been seen in a wildlife park. It is not known how widespread the practice of feed supplementation of animals in zoos and game parks has been but several species may be susceptible to BSE [see 3.2] and limited new infections with BSE could arise. The possibility of transfer to other species is discussed in 5.2 and 5.3. It cannot automatically be assumed that animals and man will react to BSE agent exposure as they have done to scrapie, which in the human case has not led to any clear association with disease [see 3.5 to 3.7]. BSE agent may for example be an adapted or particularly virulent form of scrapie agent although the results of the epidemiological study indicate otherwise [see 4.2.9].

6.4 Zoonoses

Zoonoses are diseases of animals which present a risk to human health through a pathway of infection. Many diseases have arisen in this way for a large number of pathogens can infect man as well as animals (49). Brucellosis and bovine tuberculosis (TB) are examples that have been of great concern in the recent past in Great Britain. At present the common zoonoses in Britain are salmonella, listeria and campylobacter food-poisoning. Changes in the habits of humans lead to the opening up of new pathways of infection and predispose to the emergence of new zoonoses. The increased efficiency of modern agriculture has in part been achieved by its intensification and by short-circuiting natural pathways, as, for example in recycling animal waste, i.e. feeding animal waste to chickens, cattle and pigs. Such procedures have many advantages: they reduce the loss of nutrients and they increase the growth or output of the animals, whilst at the same time disposing of waste materials that are themselves potential health hazards and pollutants. However ruminants are not by nature scavengers, thus unlike hyaenas, foxes or vultures they will not have evolved defences against the transfer of pathogens from animal wastes; as the Royal Commission on Environmental Pollution warned in its 7th Report (47) ..."the major problem encountered in this recycling process is the risk of transmitting disease-bearing pathogens to stock and thence to humans" (para. 5.63). Some recent zoonoses, like bovine TB and brucellosis, have been controlled but strict measures are often needed to eliminate the risk to humans from these animal disorders.
7. ACTIONS ALREADY TAKEN TO REDUCE SPREAD OF DISEASE

7.1 Feed Prohibition

7.1.1 In the light of the findings of the epidemiological study the Government indicated in May 1988 that it would introduce legislation (the Bovine Spongiform Encephalopathy Order 1988) which would prohibit the sale, supply or feeding of rations containing animal protein, derived from ruminants, to cattle and other ruminant animals. This action was greatly welcomed by the Working Party which had just been established. The order became effective from 18 July 1988.

7.1.2 Legislation (The Bovine Spongiform Encephalopathy (No. 2) Order 1988) has since been introduced which extends the prohibition on the use of ruminant-based feed for a further year i.e. throughout 1989. Based on a survey of the processes operated in rendering plants in Great Britain, and the available data on the activity of "unconventional agents" after various heat treatments [Appendix 1 and para. 3.9], we consider that there is no way of being wholly sure that rendering as practised would eliminate the agent. Accordingly we recommended that the ban on the use of ruminant-based protein in ruminant rations be extended indefinitely, believing that this would indicate to the industry that there can be no return to unmodified earlier practices. The original prohibition was time-limited from 18 July to the end of 1988. The Government decided that rather than make the ban indefinite, as the Working Party recommended, it would be preferable to extend it for a year. During this time further consideration will be given to the time/temperature combinations which are necessary to destroy the agent which causes BSE. If these can be determined it may be possible by adapting some of the previous rendering processes to produce a safe product. On this issue the Working Party were reassured by the Minister's statement that the prohibition would have to continue beyond the end of 1989 unless processing methods which are sufficient to destroy the agent have been identified and are widely available. The Working Party wishes to emphasise the need to be completely confident that the agent has been destroyed and must point to the difficulties of demonstrating this in view of the nature of the agent and the time taken for the symptoms to manifest themselves, even in the mouse model [see 3.8 and 3.9].

7.2 Destruction of carcases of cattle affected with BSE

7.2.1 On 7 July 1988 the Ministry of Agriculture, Fisheries and Food announced that a compulsory slaughter-with-compensation policy would be introduced following the interim advice from the Working Party. The new arrangements came into force on 8 August 1988. Under them, cattle with a clinical picture of BSE are compulsorily slaughtered and disposed of either by incineration or burial. Before disposal the head is removed so that the brain can be examined to establish a definitive diagnosis.

7.2.2 Compensation is paid at 50% of the market value of the animal, as if it were not affected with BSE, up to a ceiling. Should the disease not be confirmed following examination of the brain tissue, 100% compensation is paid. The legislation covering compulsory slaughter and the payment of compensation is contained in the Bovine Spongiform Encephalopathy (No 2) Order 1988 and the Bovine Spongiform Encephalopathy (Compensation) Order 1988.
7.2.3 It has been suggested that because compensation is set at 50% some farmers are evading the law and that as a result the carcases of affected animals are reaching the human food chain. However the evidence does not support this view. The number of suspect cases being reported has gone up since the compulsory slaughter programme was introduced. It also seems likely that should a farmer try to sell an animal for slaughter, rather than report suspected BSE, the transportation to a market and abattoir will exacerbate the clinical signs of the disease [2.3]. In these circumstances the animal will probably be reported at the market or slaughterhouse through surveillance. In fact from 21 June 1988 to the end of the year BSE was confirmed in only 40 out of a total of 63 suspect cases reported from markets and slaughterhouses. None of these cases was from herds in which BSE had previously been recognised: so there was no evidence that early signs had been suspected and that evasion was deliberate.

7.3 Milk from Cattle with suspected BSE

Although the transmission of BSE via milk is very unlikely, indeed milk has never been shown to able to transmit any of the other spongiform encephalopathies, the working party recommended at its second meeting that as a precautionary measure the milk from cattle in which BSE was suspected should be destroyed. The Government accepted this recommendation. Legislation (The Bovine Spongiform Encephalopathy (NP. 2) Order 1988) came into force on 30 December 1988 prohibiting the sale or use of milk from suspect animals for human or animal consumption, the exception being for the feeding of the cow’s own calf. The exception is made in view of the practical and welfare problems which could well arise should there be a legal requirement to remove the calf at the time of birth.

8. FURTHER RECOMMENDATIONS

8.1 Monitoring of offspring of affected animals

The eventual size of the BSE epidemic [see section 6] will depend very largely on whether or not the cow is a dead-end host. If this is the case, and the action taken as described in 7.1 and 7.2 has stopped new infections, the disease should die out as the cohorts of infected animals develop BSE and are destroyed. It is essential that enough offspring of cows known to have had or to have subsequently developed BSE are monitored to enable evidence for or against vertical transmission to be obtained. Three hundred such offspring with an equivalent number of controls have been identified by the Ministry [see 5.1.1]; the Working Party urge that all necessary resources are made available to ensure that these animals are monitored and that they are not destroyed before they are old enough to display the disease, should they be infected. Premature loss of these animals could delay for some years acquisition of evidence about vertical transmission in cattle.

8.2 Medicinal Products

Consideration has been given to the potential for the transmission of BSE between cattle and other species, including man, through the use of medicinal products [see paragraph 5.3.3]. Although the risks appear remote the Working Party recommended that the attention of the Licensing Authority, the Committee on Safety of Medicines (CSM), the Committee on Dental and Surgical Materials and the Veterinary Products Committee (VPC) be drawn to the emergence of BSE so that they can take appropriate action. In this connection the Chairman of the Working Party has corresponded with the Chairman
of the CSM and with the VPC [Appendix 3].

8.3 Health and Safety

Paragraph 5.3.4 draws attention to a number of occupational groups, such as veterinarians, slaughtermen, herdsmen and laboratory workers, who could conceivably be exposed to the BSE agent. It is recommended that the potential problems caused by BSE are brought to the attention of the Health and Safety Executive who can consider whether further guidance should be given to such groups.

8.4 Surveillance

Monitoring of cases of Creutzfeldt-Jakob Disease should take place, both through the neurological network and by OPCS, since any human cases of BSE would present as CJD [see para 5.3.6 above].

8.5 Research

8.5.1 The Working Party has discussed a number of areas of research which it considers essential if progress is to be made in our understanding about the disease and how to deal with it. In the first interim report from the Working Party we recommended that a new committee should be set up to advise, co-ordinate and oversee the research work needed in this field. This recommendation has been accepted. An expert Consultative Committee on Research has now been established. The membership is:-

Dr D Tyrrell CBE, FRS - Director MRC Common Cold Unit
(Chairman)

Dr W A Watson - Director of the Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food

Professor J Bourne - Director of the Institute of Animal Health

Dr R J Will - Consultant Neurologist at the Western General Hospital, Edinburgh

Dr R Kimberlin - Ex-Director of the Neuropathogenesis Unit Edinburgh

Its terms of reference are:-

1. "To advise the Ministry of Agriculture, Fisheries and Food and Department of Health on research on transmissible spongiform encephalopathies including:-
   a. work already in progress or proposed;
   b. any additional work required
   c. priorities for future relevant research.

2. In the context of these terms of reference transmissible spongiform encephalopathies includes those affecting both domestic and wild ruminants and man".
8.5.2 Areas of research which this Working Party believes should be considered are:

(i) Epidemiological Studies - in particular to examine further the role of meat and bone meal as the source of BSE and to determine whether or not maternal (vertical) and horizontal transmission can take place.

(ii) Transmission studies in a variety of possible host species. Transmission to mice has already been demonstrated at the MRC/AFRC Neuropathogenesis Unit. We understand that other studies are underway or planned using cattle, marmosets, hamsters, mink and goats. Parallel cattle studies are also planned using the scrapie agent. Further projects are planned, using material from affected cattle, to determine whether or not transmission is possible via semen and embryos. Follow-up studies should be designed to determine the physical and chemical processes to which the agent is susceptible and thus the conditions required to make material (such as rendered infected carcases) "safe".

(iii) Transmission experiments using muscle and milk, in the latter case to repeat earlier experiments which showed that milk was not a vehicle for scrapie transmission to any species.

(iv) Possibility of formal monitoring of the health of pigs and domestic pets, particularly since pigs are used in the manufacture of some pharmaceuticals. Transmission experiments may be relevant for some of these species. We assume that there is no intention to exclude these animals from the Committee's terms of reference, and believe that the departments concerned will recognise the dangers of excluding these potential infective pathways.

(v) Studies to determine whether the BSE agent is identical in its molecular structure to the natural agent of scrapie or modified in some way. Determine whether there are single or multiple strains and the relationship to agents responsible for transmissible encephalopathies in other species.

(vi) The determination of the nature of the infectious agent: clearly this would be a tremendous breakthrough as would a means of positively identifying the infection in sub-clinical form. However, the difficulties of achieving this are acknowledged and the scrapie experience exemplifies the difficulties of making progress in this direction.

(vii) Genetic studies to determine whether there are any genetic factors involved in the disease expression in cattle.

(viii) The surveillance of humans at particular "risk" and formal monitoring of CJD cases, particularly in occupational groups exposed to bovine tissues.

8.5.3 The Working Party regards research as essential, for if there is any vertical or horizontal transmission the results will have a critical bearing on whether or not there is sufficient understanding of the disease to be able to control and eventually eliminate it. It will also have vital implications in terms of the ability or otherwise to maintain our important export trade in cattle, semen and embryos. And above all it may lead to complete reassurance about the lack of risk to human health or point the way to eliminating practices that could open up new pathways for infection.
9. GENERAL CONCLUSIONS

9.1 Bovine spongiform encephalopathy belongs to a group of diseases that are particularly intractable: the precise nature of the causative sub-viral agent is uncertain, their incubation periods are long, diagnosis is difficult except in the terminal stages and the mechanisms of transmission are variable and often obscure. One such disease, scrapie, has been widespread in sheep flocks in Britain and in other countries for at least two centuries, whilst CJD, a human encephalopathy with a worldwide distribution, has remained rare.

9.2 From present evidence, it is likely that cattle will prove to be a "dead-end host" for the disease agent and most unlikely that BSE will have any implications for human health. Nevertheless, if our assessments of these likelihoods are incorrect, the implications would be extremely serious. Thus, we greatly welcome the speed with which the Ministry of Agriculture, Fisheries and Food has brought forward regulations based on the veterinary evidence and on our recommendations and are encouraged by what we have learned of the positive response from the animal foods and farming industries to ensure the effectiveness of the regulations.

9.3 Assuming there is no vertical or horizontal transmission, the strict adherence to the regulations preventing the incorporation of infective material in calf and cattle feed should (after about 4 years) lead to a fall in the number of new cases and, on present evidence, after about 9 years the disease is likely to be extinct in Great Britain. In the meantime, farmers will have to exercise continual vigilance to ensure that animals exhibiting early symptoms are identified and prevented from entering the human food chain.

9.4 This problem has arisen as a result of the practice of feeding ruminant materials to herbivores, which are thus exposed to infective risks against which they have not evolved any defences. Such practices are a feature of modern intensive agriculture, but inevitably (as with BSE, and bacterial pathogens in poultry) they open up new pathways for infection to the farmed animals and potentially from them to man, via food and/or medicinal products. We note that animal meal supplements do increase the rate of growth of the animals, whilst also providing a superficially efficient way of disposing of animal waste. But we believe that the risks from inadequately sterilised animal products are such that this method of disposing animal waste should be changed so as to eliminate these novel pathways for pathogens. We urge Ministers to address this general problem as part of the adjustment of the framework of the agricultural policy of the EC in the coming years.
10. **SUMMARY**

10.1 We were asked to advise the Ministry of Agriculture, Fisheries and Food and the Department of Health on "the implications of Bovine Spongiform Encephalopathy and matters relating thereto" [1.1, 1.3].

10.2 We have concluded that bovine spongiform encephalopathy (BSE) is one of the transmissible encephalopathies caused by an unconventional infectious agent with a prolonged incubation period [3.1]. The epidemiological evidence suggests this new disease has appeared as a result of contamination of meat and bone meal derived partly from sheep offal and fed to British cattle from the early 1980's. Contamination had arisen because modern rendering practices failed to destroy the agent of scrapie, the endemic spongiform encephalopathy of sheep [4.2].

10.3 To prevent further infection in cattle the use of ruminant-based protein in ruminant rations has been banned [7.1]; we recommended that this ban be continued indefinitely [7.1.2].

10.4 Concerned at the remote chance that this new infection could be transmitted orally to man, we recommended the destruction of carcases of cattle with suspected BSE [7.2] and prohibition of the use of milk from such cows for humans [7.3]. These recommendations have already been acted upon.

10.5 Considering other possible routes of transmission we have drawn the attention of the Licensing Authority to the potential of transfer of BSE agent in human and veterinary medicinal products [8.2]. We draw the attention of the Health and Safety Executive to possible exposure of various occupational groups to BSE agent [8.3]. We ask that specialist branches of the medical profession be alerted to the possible emergence of a new spongiform encephalopathy presenting as Creutzfeldt-Jakob disease [5.3.6].

10.6 Our deliberations have been limited by the paucity of the available evidence. Further research work in this area is essential. We recommend that the new Consultative Committee on Research coordinates investigations in this field [8.5.1] and we make suggestions for studies in the areas we consider to have special priority [8.5.2]. We stress the particular importance of continuation of a study of possible transmission in cattle [8.1].

10.7 We note that this disease appears to have originated from unnatural feeding practices as found in modern agriculture. We question the wisdom of methods which may expose susceptible species of animals to pathogens and ask for this general issue to be addressed [9.4].

R Southwood (Chairman)
M A Epstein
W B Martin
J Walton

22
Pre April 88  Post June 88

Duration of Illness: months

% of cases

Cases of BSE

Distribution of confirmed cases of BSE

FIGURE 1
### FIGURE 2

<table>
<thead>
<tr>
<th>AGE (yr)</th>
<th>1987*</th>
<th>1988*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. animals at risk</td>
<td>No. cases</td>
</tr>
<tr>
<td>2</td>
<td>2441</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4534</td>
<td>52</td>
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<td>4</td>
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<td>9</td>
</tr>
<tr>
<td>7</td>
<td>2031</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>1343</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>826</td>
<td>0</td>
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<td>Unknown</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>TOTAL</td>
<td>21910</td>
<td>270</td>
</tr>
</tbody>
</table>

*based on: 188 herds in 1987
1181 herds in 1988

Age specific incidences of confirmed and clinically suspect cases during 1987 and 1988 within herds in which at least one case of BSE has been confirmed histopathologically.
FIGURE 3

INCIDENCE (%) OF DAIRY HERDS WITH CONFIRMED BSE
NOVEMBER 1986 TO DECEMBER 1988

Incidence %

- 0 to 0.09
- 0.1 to 1.99
- 2 to 3.99
- 4 to 5.99
- 6 to 9.99
- 10 to 18
**INCIDENCE OF BSE AFFECTED DAIRY HERDS (up to 31st Dec '88)**

<table>
<thead>
<tr>
<th>COUNTY</th>
<th>NUMBER OF DAIRY HERDS AFFECTED</th>
<th>NUMBER OF DAIRY HERDS AT RISK</th>
<th>INCIDENCE % HERDS</th>
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<tr>
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<td>131</td>
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<td>BUCKS</td>
<td>13</td>
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<td>I.O.W</td>
<td>8</td>
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<td>35</td>
<td>320</td>
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<td>23</td>
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<td>45</td>
<td>332</td>
<td>13.6</td>
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<td>2178</td>
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<td>54</td>
<td>733</td>
<td>7.4</td>
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<td>SOMERSET</td>
<td>108</td>
<td>2021</td>
<td>5.3</td>
</tr>
<tr>
<td>WILTS</td>
<td>71</td>
<td>1025</td>
<td>6.9</td>
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<td>1.1</td>
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<td>268</td>
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<td>228</td>
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<tr>
<td>YORKS N</td>
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<td>2456</td>
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<tr>
<td>YORKS W</td>
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<td>YORKS W</td>
<td>8</td>
<td>623</td>
<td>1.3</td>
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<td></td>
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<tr>
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<td>1323</td>
<td>1.1</td>
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<tr>
<td>HEREFORD &amp; WORCESTER</td>
<td>33</td>
<td>908</td>
<td>3.6</td>
</tr>
<tr>
<td>LANCS</td>
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<td>1.8</td>
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<tr>
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<td>5.0</td>
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<td>43</td>
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<tr>
<td>NOTTS</td>
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<td>237</td>
<td>2.5</td>
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<td>1499</td>
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<td>1.7</td>
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<td>2.9</td>
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<td>1.7</td>
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<td>6.9</td>
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<td>109</td>
<td>7178</td>
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</tr>
<tr>
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<td><strong>OTHERS</strong></td>
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<tr>
<td>ISLE OF MAN</td>
<td>3</td>
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<tr>
<td>GUERNSEY</td>
<td>15</td>
<td>87</td>
<td>17.2</td>
</tr>
<tr>
<td>JERSEY</td>
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<td>110</td>
<td>0</td>
</tr>
<tr>
<td><strong>all cattle herds</strong></td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Month/year onset of clinical signs

Incomplete data containing suspect cases not yet confirmed. There will also be many additional cases for these months which have not yet been diagnosed or suspected; the final total will be higher.

YEAR OF ONSET
DISTRIIBUTION OF BBF CASES BY MONTH AND

FIGURE 5

722 cases; onset date unknown
27
12. REFERENCES


28


47. Royal Commission on Environmental Pollution. Agriculture and Pollution. Seventh Report (1979); Cmdnd 7644 HMSO (280pp)


30


APPENDIX 1

RENDERING IN GREAT BRITAIN

1. Rendering is a cooking and separating process whereby animal waste is sterilised and fats and protein extracted. Up to 80% of the material for rendering comes from abattoirs and boning-out plants, around 10% from retailers such as butchers and 10% from knackers, restaurants, kennels etc. The end products of rendering are edible fats, which are derived from edible fat inputs and processed separately from non-edible material, and tallow and meat and bone meal derived from non-edible material. Greaves are an intermediate solid product which is further processed into meat and bone meal.

Tallows are used for soap manufacture, fat splitting and animal feeds and were the traditional main products of the rendering process. The nutritional value of meat and bone meal was realised in the early 1920's and in the post war years has been used in animal feedstuffs.

2. In 1988 there were 41 rendering plants in Great Britain in operation producing tallow and greaves, and in many cases further processing the greaves to produce meat and bone meal. Through the helpful cooperation of the plant owners and the UK Renderers Association detailed information on these plants was obtained during 1988 by the State Veterinary Service. The following is a summary of these findings.

3. 1.3 million tonnes of raw material are processed by these plants each year. This material comprises 15.9 per cent fat, 30.5 per cent bones, 33.4 per cent offal, 8.9 per cent carcases and 11.5 per cent of other mixed material. The species composition of this material was estimated to be at 44.8 per cent bovine, 15.3 per cent ovine, 20.9 per cent porcine and 19.0 per cent of mixed origin including poultry.

The output of these plants in 1988 was 350,000 tonnes of meat and bone meal and 230,000 tonnes of tallow.

4. Batch rendering, the traditional method of cooking, is used by 28 plants involving some 26,000 tonnes of material per month. The mean particle size of material entering these cookers is 10 cm. Commonly each batch is heated for 1.5 to 2 hours to maximum temperatures ranging from 102 to 150°C under atmospheric pressure. In some plants the load is discharged once the maximum temperature is reached, in others there may be a holding time of up to 30 minutes.

5. Continuous rendering is used by the remaining 13 plants which process more than 70,000 tonnes of material per month. The first such plants were installed in the early 1970's. The mean particle size of material entering these cookers is 3cm.

a. Stork Duke Cookers
Temperatures of 135 to 145°C are achieved in the 5 cookers of this type. Independent studies have indicated that the residence time in these cookers is just over an hour.

*see Monopolies and Mergers Commission report (1988)
b. Stord Bartz Driers
Temperatures of between 80 and 145°C are achieved in the 9 cookers of this type. Experiments at one plant indicated a minimum residence time of 60 minutes with an average of 2.5 hours. The exposure to maximum temperatures occurred two thirds of the way along the cooker giving an exposure to this temperature for about 35 minutes.

c. Carver Greenfield Systems
There are three plants of this type which heat material for 30 to 40 minutes to a maximum of 104 to 123°C and being at the maximum temperature for approximately 15 minutes. Recycling occurs in this process.

d. Protech System
Two new plants using this system have been commissioned recently. Minced raw material is heated to 95°C for 3 to 7 minutes. The solids are then dried in one plant in hot air which starts at 800 to 900°C and finishes at 110°C, and in the other in batch cookers at 120 to 130°C.

6. Comment from the Working Party
There is a lack of hard information on the time-temperature profiles in rendering plants under normal operating conditions, and no information on the usual extreme ranges that might be encountered. (The lowest temperatures for the shortest time are the most critical conditions). However, whereas any heat treatment might be expected to reduce the infectivity of scrapie agent somewhat, none of the current processes would appear capable of eliminating all strains of scrapie agent. Under unfavourable conditions, the time-temperatures might even not be adequate for all the more usual pathogenic organisms.
APPENDIX 2

EVIDENCE RECEIVED BY THE WORKING PARTY

20 June, 10 November, 16 December, 1988, 3 February 1989: oral and written evidence from Mr J. Wilesmith.

1 September, 23 September, 17 October and 2 December: correspondence from Dr D. Doyle, consultant neuropathologist concerning epidemiology of BSE and human spongiform encephalopathies, unusual cases of CJD, compensation for BSE and exposure to BSE during veterinary pathological examinations.

19 October 1988: prepublication draft sent by Dr H Fraser of the Neuropathogenesis Unit, Edinburgh.

27 October 1988: letter from Dr E. Poole, EEG Department, The Radcliffe Infirmary, Oxford on how BSE might present in humans.

2 November 1988: report from the Chief Veterinary Officer of an investigation into rendering plants in Great Britain.

4 November 1988: report and draft publications from Dr J. Hope of the Neuropathogenesis Unit, Edinburgh.

10 November: oral evidence from Dr R. Kimberlin, formerly of the Neuropathogenesis Unit, Edinburgh.

1 December 1988: Report from Mr B. Aldridge on published and pre-publication studies on BSE from the Royal (Dick) School of Veterinary Studies, Edinburgh.

2 December 1988: report from the Chief Medical Officer on CJD in human growth hormone recipients.

13 December 1988: letter from Mr B. Ahern, farmer in Taunton, concerning early cases in his herd.

2 January 1989: Prepublication report from Drs W.C. Foote (Utah State University) & J.R Pitcher (Texas) on scrapie in USA.

1 February 1989: Comments on specific issues by Dr J T Hughes, Department of Neuropathology, Radcliffe Infirmary, Oxford.

3 February 1989: Evidence from the Ministry of Agriculture, Fisheries and Food on the rendering industry.
APPENDIX 3

OFFICIAL CORRESPONDENCE FROM THE WORKING PARTY

21 June 1988: letter from Chairman to Mr D Andrews, Permanent Secretary (MAFF) with interim recommendations from first meeting of the working party.

14 November 1988: letter from chairman to Mr D Andrews (MAFF) with interim recommendations from second meeting of the working party

14 November, 7 December and 23 December 1988: correspondence with Professor Asscher, chairman of CSM

20 December 1988: letter from chairman to Mr Andrews (MAFF) about monitoring of offspring of cattle affected with BSE

20 December 1988: letter to Dr T Little, Veterinary Products Committee.

16 August 1988: letter from secretariat to Dr J S Ashley, OPCS.

24 June and 15 November 1988: letters from secretariat to Dr D Gompertz, Health and Safety Executive.

ABBREVIATIONS USED

BSE: Bovine spongiform encephalopathy
CJD: Creutzfeldt-Jakob disease
CSM: Committee on Safety of Medicines
EEG: Electro-encephalogram
MAFF: Ministry of Agriculture, Fisheries and Food
MRC: Medical Research Council
OPCS: Office of Population Censuses and Surveys
SAF: scrapie associated fibrils
TB: tuberculosis
TME: transmissible mink encephalopathy
VPC: Veterinary Products committee