12. Science and research

1117 Although only one member of our Committee is a scientist, our terms of reference have required us to review, at second hand, a substantial body of scientific learning and research. We are required to establish the history of the emergence of BSE. In order to attempt to answer the questions of where BSE came from and why it emerged in this country we have had to consider, among other things:

- epidemiological research;
- evidence on the technical aspects of rendering and the inactivating effect of rendering processes on TSE agents;
- transmission properties of BSE compared with those of scrapie; and
- strain-typing of the BSE agent after transmission to mice.

1118 More fundamentally, we have had to consider the complex research on the very nature of TSEs. This is critical to the theory, now widely accepted, that BSE has been transmitted as a result of recycling bovine protein that included infective prion protein.

1119 In the course of our Inquiry we have received evidence from scientists who espouse alternative theories, for example:

- the organophosphate theory; and
- the autoimmune theory.

We have had to consider whether these were viable alternatives to the prion protein theory.

1120 More generally, our requirement to review the adequacy of the response to BSE, taking into account ‘the state of knowledge at the time’, has required us to follow the development of scientific knowledge about BSE between 1986 and 1996, paying particular attention to those aspects which had a bearing on the likelihood that BSE might be transmissible to man.

1121 We are also required to establish the history of the emergence of vCJD. This has required us to consider the scientific research, both before and after 20 March 1996, which has focused on the question of whether the link between BSE and vCJD is clearly established.

Scientific conclusions about BSE

1122 Our analysis of the scientific knowledge occupies the major part of vol. 2: Science. We shall not attempt a summary in this volume. We shall simply set out the conclusions that we have drawn from the scientific response to BSE:
i. **The vector responsible for the epidemic of BSE in cattle was MBM**

The spread of BSE in cattle to the point where it became an epidemic came about from the use of meat and bone meal (MBM) in cattle feed. The MBM in question was infective because it had been made by rendering infective offal from cattle suffering from, or merely incubating, the disease. As little as 1 gram (or less) of this material could cause death if ingested by other cattle. It was so infective that accidental contamination of cattle feed with pig or poultry feed containing MBM was a significant factor in continuing to spread BSE after the ban on the use of MBM in cattle feed. Apart from MBM in feed, transmission from mother to calf is likely to have played a part. We cannot yet say whether contamination of pastures played a part. The suggestion has been made that the BSE agent may have been spread in the early stages in hormones used in veterinary preparations. This possibility cannot be discounted. But the overwhelming vector of the epidemic was MBM in cattle feed.

ii. **The unmodified scrapie agents were not the agents responsible for BSE**

While it was reasonable in February 1989 to accept the hypothesis that the cases of BSE being reported had come about through the rendering of carcasses of sheep infected with extant strains of scrapie established in the national flock, this theory is no longer plausible. We think it likely that the passive surveillance system failed to detect several earlier cycles of BSE in the South West of England in the 1970s and early 1980s. Each cycle was followed by more extensive contamination of MBM. Much of the recycling could not be detected because tissues from animals incubating the disease but not showing signs were involved; but it is likely that there were isolated animals which did develop signs and were slaughtered or died of the disease. BSE was unknown at the time and it seems possible that the disease in such cattle might have been ascribed to known disorders such as hypomagnesaemia or simply not explored. These early cycles began because a novel TSE agent originated in the early 1970s. The cause of this novel agent is likely to have been a new prion mutation in cattle, or possibly sheep. Moreover, other mammalian species whose carcass waste was included in MBM cannot be excluded. It is conceivable that the conversion of normal prion protein into its infective form was initiated not by a gene mutation, but by an environmental agent, such as a toxic chemical; this has not yet been achieved experimentally. Current knowledge suggests that the original agent was not the unmodified scrapie agent or agents. We have also noted a number of pointers which could have led to the conclusion by mid-1990, and certainly well before 20 March 1996, that the agent fuelling the BSE epidemic was not then (if it ever had been) the unmodified scrapie agent or agents. It is now not possible to be sure which of the hypotheses as to the origin of the novel agent is correct.

iii. **Changes in rendering**

It is a common misconception that reduction in temperature or a failure to prescribe minimum holding times in the rendering of carcass waste led to failure of inactivation of the scrapie agent and transmission across the
species barrier to cattle. Changes in the rendering process in the late 1970s and early 1980s, namely the switch from batch to continuous processing and the abandonment of solvent extraction of tallow, might have led to reduction in inactivation of the agent in MBM, but it is now known that the processes used previously were also incapable of completely inactivating TSE agents. No commercial rendering procedure has been designed capable of completely inactivating BSE in MBM before or since.

iv. Confirmation of the central role of prion protein

All evidence points to the specific association of an abnormal form of the prion protein and TSEs. In its normal shape, the prion protein (PrP\text{C}) does not cause harm. In its abnormal shape (signified by PrP\text{Sc} – a generic term for the agents causing TSEs), it is resistant to the normal cellular processes of degradation. Contact between normally shaped and abnormally shaped proteins induces the normal to convert to the abnormal. This leads to a build-up of the abnormal form of the protein, which accumulates in, and eventually causes the death of, nerve cells. Nerve cells are particularly susceptible to PrP\text{Sc} because they cannot regenerate. The presence of PrP\text{Sc} can be demonstrated in the brain and spinal cord of all humans and animals affected with TSEs. Incubation times in experimental animals correlate with the infective dose of the agent, and these times are increased by treatment with agents (β-sheet breaker peptides) which reverse the conformational change leading to PrP\text{Sc}. These observations virtually eliminate other hypotheses as to the direct cause of TSEs, such as autoimmune disease of the central nervous system, because those hypotheses do not incriminate the prion protein. In both scrapie and vCJD, susceptibility and resistance to disease is associated with polymorphisms within the prion protein gene (though no such genetic susceptibility factors have yet been identified for BSE). It remains possible that environmental factors, including toxic chemicals, may additionally be implicated in susceptibility to prion disease.

v. BSE is caused by a single strain of agent

Strain-typing in mice has shown that all sources of the BSE agent so far examined produce the same lesion profile and incubation times in experimental mice. The same strain has been identified in cats, which have developed FSE since 1990, and in exotic ungulates and carnivores from zoological parks.

vi. Variant CJD is caused by the BSE agent

Strain-typing studies in mice reveal that the disease patterns produced by the agents causing BSE and vCJD are identical. The glycosylation patterns of the prion protein associated with each condition are also identical and different from other TSE strains. In transgenic mice in which the mouse prion gene has been replaced by the bovine prion gene, inoculation with the BSE agent from cattle brain produces the same disease pattern and incubation period as agent derived from patients with vCJD. Following inoculation with the scrapie agent, the incubation period and disease patterns in the transgenic mice are markedly different from those produced by BSE.
and vCJD. In the absence of any other plausible factor, the evidence that BSE caused vCJD is so strong that all other hypotheses are now excluded.

**Alternative theories**

**The organophosphate theory**

1123 The theory that BSE was caused by a reaction to the use of organophosphorus compounds (OPs) poured on cattle as systemic pesticides cannot be reconciled with the epidemiology and is not supported by research. One experiment has, however, given some limited support to the possibility that the OP phosmet might modify the susceptibility of cells to the prion disease agent.

**The autoimmune theory**

1124 There are a number of reasons why this theory does not seem viable, including:

- the fact that mouse-adapted BSE can be transmitted by intracerebral inoculation to mice lacking a functional immune system; and
- the fact that the theory is incompatible with what has been established about the central role of the prion protein in TSEs.

**Research**

1125 An important aspect of the response to BSE was the research that was undertaken in order to learn more about the disease. Before 20 March 1996 MAFF had funded over 120 research projects in relation to different aspects of BSE. Research work into TSEs, and more particularly BSE, was also funded by the Research Councils. We have not interpreted our terms of reference as requiring us to review the adequacy of all these projects. What we have explored are the broader questions of the funding, planning and coordination of BSE research. Our consideration of these topics is to be found in vol. 2: *Science* and vol. 11: *Scientists after Southwood*. Here we propose to do no more than set out a brief summary of our conclusions.

1126 BSE did not emerge at a propitious time so far as research was concerned. In 1985 Ministers had accepted a recommendation from the Priorities Board for Research and Development in Agriculture and Food that expenditure on research into animal diseases was disproportionate and should be reduced by 20 per cent. Implementation of this policy was resulting in staffing cuts at research establishments.

1127 The Neuropathogenesis Unit (NPU) in Edinburgh had been set up jointly by the Agricultural and Food Research Council (AFRC) and the Medical Research Council (MRC) in 1981 as an independent unit to study scrapie and the similar
human diseases of the central nervous system such as CJD. The need to relocate staff and facilities and to build up suitable mouse colonies, coupled with financial constraints on the appointment of necessary new staff, meant that it had not yet been able fully to address this remit, although it had brought together a wide range of expertise in genetics, strain characterisation and transmission of scrapie. In 1986, however, it had been brought within the framework of the Institute for Research on Animal Diseases, later to become the Institute for Animal Health. Shortage of funding and the loss of independence had resulted in the disillusionment of its Director, Dr Alan Dickinson, who resigned in 1987, and for whom for a long time it proved impossible to find a suitable replacement. There was also uncertainty about where the various parts of the new Institute should be located. Thus the emergence of BSE found the NPU in a state of some disarray and with its future in doubt.

1128 Despite these problems, both at the NPU and more generally, research into BSE was not significantly impeded through lack of funding, although some research projects got off to a slow start. An application for additional funds from the Treasury Reserve was laboriously put together, finally presented in August 1989 and rejected. Alternative sources of funding were then identified, which involved the diversion to BSE of funding earmarked for other projects.

1129 Between 1987 and 1996 the Government spent over £60 million on research into BSE and other TSEs. Of this, £37.9 million was spent by MAFF and £27.4 million funded by the Research Councils. DH’s expenditure was £1.6 million, largely spent on funding the CJD Surveillance Unit (CJDSU).

1130 Almost all the research funded by MAFF was carried out either at the CVL or at the NPU, with CJD research being carried out by the CJDSU. The BSE research programme was developed within the CVL by the BSE Group, headed by Mr Bradley, in consultation with the NPU. One project involved collaborative work between the two laboratories. Priorities were allocated by the Tyrrell Committee. The research that was carried out was extensive and wide-ranging, for example:

- It identified that BSE had the histopathology of a TSE.
- It quickly identified that BSE was transmissible to mice, both by inoculation and in feed.
- It identified that BSE was similarly transmissible to sheep and to goats.
- It confirmed the infectivity of brain and spinal cord and identified the infectivity of the distal ileum of calves.
- It identified that ½ gram would suffice to transmit BSE orally to a sheep and 1 gram to a calf.
- It identified the fact that BSE was a single and distinctive strain of TSE agent.
- It swiftly identified the emergence of a new variant of CJD.
- It identified the link between vCJD and BSE.

1131 In 1990 Sir Donald Acheson set in train an initiative to place the AFRC/MAFF/MRC research effort on BSE under the coordination of a single ‘director’.
This met with resistance on the part of the Research Councils, which saw it as a threat to their independence, and was supported by MAFF only on condition that the director would report to the MAFF Minister. The proposal foundered. Instead it was agreed that SEAC would perform a limited role in facilitating interchange between the various bodies responsible for research. The demands on SEAC for advice were so onerous that members did not have the time to carry out a review of the adequacy of the research effort and to identify gaps in the research programme. The most that they were able to do was to check that the projects recommended by the Tyrrell Committee as having high priority were under way. In June 1992 they published a paper that recorded that they were ‘content with the progress of implementing the recommendations overall’.

1132 We have concluded that it might have been advantageous to have had an individual or committee with a remit to coordinate research and to draw attention to research needs. As it was, these were largely identified by the CVL, which then played the role of contractor in supplying much of the research identified. Thus most of the projects were awarded without competition and were not peer-reviewed. We have identified, with hindsight, areas where research could profitably have been started earlier or been pursued with more vigour. Also, an attempt might have been made with advantage to recruit expertise from the wider scientific community. It is at least possible that had an overview been kept of all BSE research, some of these issues would have been identified and addressed at the time:

1133 Scrapie-into-cattle transmission – Experiments to see if and how scrapie would transmit to cattle were begun in 1997. It would have been valuable to test the theory that BSE was caused by the scrapie agent or agents ten years earlier, although we accept that there were difficulties in the way of doing this.

1134 BSE in sheep – The possibility that BSE might have been transmitted to sheep was recognised as early as 1987. So too was the risk that, if it had done so, it, like scrapie, might become endemic in sheep. Research to check whether this has happened is now being carried out. It is perhaps the most important unanswered question about the BSE epidemic.

1135 Minimum infective dose – The NPU experiment to transmit BSE to sheep and goats, which was initiated in 1988, was, incidentally, a valuable test of whether a dose as small as that contained in ½ gram of material would transmit in feed across the species barrier. It was not, however, designed or used for the purpose of providing this information. The 1992 attack rate experiment was the first occasion on which MAFF sought to see how much infective material was needed to transmit BSE in feed, and even this was not designed to identify the minimum quantity. The results of the attack rate study were of great practical importance.

1136 Sensitivity of the mouse bioassay – the infectivity of different tissues in BSE-infected cattle was tested by bioassay in mice. Tests begun in 1993 have demonstrated that mice are at least 1,000 times less susceptible to BSE than cattle. It would have been advantageous if the extent of this species barrier had been identified earlier.

1137 Ante- and post-mortem tests for BSE – Simple ante- and post-mortem tests for BSE would have been of the greatest practical value. These are areas which
could have been developed with greater vigour and in which a research ‘supremo’ might have stimulated open competition.

1138 *ELISA test for ruminant protein in compound feed* – Research was carried on ‘in house’ at a leisurely pace. This was in part because the importance of developing such a test was not appreciated until the significance of cross-contamination of feed was brought home in 1994. A research director might have identified external sources that would have advanced this area of research more rapidly.

1139 *Epidemiology* – One of the remarkable features of BSE research is that the epidemiology was left largely to Mr Wilesmith and the members of his small epidemiology department at the CVL. This perhaps reflected the lack of veterinarian epidemiologists in this country. There was, however, scope for human epidemiologists to address questions such as the cause of the BABs, the pattern of the epidemic and the number of subclinical cases going into the human food chain.