5. Emergence of variant CJD

Introduction

5.1 The announcement by the Government on 20 March 1996 regarding the possible link between BSE and a new variant of CJD followed consideration by the CJDSU of cases of CJD in people associated with farming and in young people. This chapter describes these cases and provides a chronological account of the CJDSU’s work leading up to the announcement. In this chapter we have identified by letter patients under 50 referred to the CJDSU before 20 March 1996. The annex to this chapter gives further information.

5.2 The final section of this chapter describes the main findings of the CJDSU, the evidence for a causal link between vCJD and BSE, and the predictions that have been made about the future incidence of vCJD.

Chronological account of the emergence of vCJD

1989

5.3 The first report of an association of a case of CJD with a farm, after the emergence of BSE in 1986, was on 13 October 1989. Dr Pickles wrote to Dr Will relaying a conversation she had with a neuropathologist. The conversation concerned a case of CJD in a woman said to be associated with a farm where there had been cases of BSE. The neuropathologist was uncertain about her age, initially claiming her to be 36, but later suggesting that she could have been older. Dr Pickles commented:

When I hear more, I will pass on the details to you, but you may hear from your own grapevine contacts in any case. Let’s hope Dr Timperley [the neuropathologist] got the age wrong by several decades. And let’s also hope the media do not hype it up before we have a chance to investigate in adequate detail. 182

5.4 Later that month, on 26 October 1989, a CJD case was mentioned in a minute from Sir Donald Acheson, (CMO) to Mr Roger (now Lord) Freeman (Minister, DH). Sir Donald informed him of the CJD case, a 60-year-old woman, who was said to be associated with a farm where there had been BSE cases. 183 (This may have been the case referred to by Dr Pickles, but this is not stated in the minute.) He noted that Dr Will would be making ‘appropriate enquiries’. 184

5.5 Sir Donald also commented upon the lack of press interest, but pointed out that if questions arose, the response would be not to comment on individual cases and reiterate that the risk was remote. He suggested using the analogy that scrapie had...
infected sheep many years ago with no ‘apparent hazard to humans’\textsuperscript{185}. The minute also advised that the Government was already taking steps in view of the remote possibility of transmission of BSE to man\textsuperscript{186}.

**5.6** The results of Dr Will’s investigations into this case were relayed by Dr Pickles on 20 November 1989 to Sir Donald. She stated that Dr Will’s conclusion was that ‘any connection between this patient and any bovine condition was tenuous’\textsuperscript{187}. She further commented that no further action was required.

**‘The first farmer’ – August 1992**

**5.7** At the beginning of August 1992, Dr Will confidentially informed Dr Ailsa Wight (DH, senior medical officer with responsibility for TSEs), that a probable case of CJD had occurred in a 60-year-old farmer whose farm, in the Manchester area, had a history of BSE. Dr Wight passed on this information to Sir Kenneth Calman (CMO) on 13 August 1992, stating that the CJD patient was alive and had been visited by the CJDSU\textsuperscript{188}. Although unconfirmed, the diagnosis was considered likely to be CJD on clinical grounds. Dr Wight advised that:

> There is no direct evidence that the two events (BSE and CJD) are linked and Dr Will feels they are probably a coincidence. Despite the rarity of CJD, it was perhaps only a matter of time before this situation arose, given the large numbers of people employed in the agricultural and related industries, and the fact that BSE cases now total over 65,000\textsuperscript{189}.

**5.8** This ‘first case’ of CJD in a cattle farmer was discussed by SEAC\textsuperscript{190} at their 13th meeting on 15 October 1992\textsuperscript{191}. Dr Will informed the meeting that one of the farmer’s cows had confirmed BSE in 1989 and that the farmer had developed CJD two years later\textsuperscript{192}.

**5.9** Dr Will informed SEAC that he intended to publish a report of his study of this case in a scientific journal ‘which would probably draw the conclusion that there was no evidence that this was not a chance occurrence of normal disease’. Dr Will also reported that his studies at the CJDSU had failed to reveal a correlation between occupational backgrounds and CJD to date\textsuperscript{193}.

**5.10** On 22 October 1992, a minute from Mr Thomas Murray (SEAC DH Secretariat) informed the Secretary of State about the SEAC meeting and the fact that the farmer had now died\textsuperscript{194}. He noted that the diagnosis of CJD had been confirmed by pathology and that the CJDSU had also ruled out iatrogenic or familial CJD, as well as exposure to cattle brain. He commented that the SEAC meeting had come ‘to the view that all indications suggested that it was a typical sporadic case of CJD. However in view of the history it is hoped to carry out further laboratory studies to try to confirm this.’

\textsuperscript{185} YB89/10.26/3.1
\textsuperscript{186} YB89/10.26/3.2
\textsuperscript{187} YB89/11.20/11.1
\textsuperscript{188} YB92/8.13/2.1–2.2
\textsuperscript{189} YB92/8.13/2.1–2.2
\textsuperscript{190} SEAC – Spongiform Encephalopathy Advisory Committee. This Committee was set up after advice from the Tyrrell Committee. Dr Will was a member of SEAC from its outset
\textsuperscript{191} YB92/10.15/2.1–2.8
\textsuperscript{192} YB92/10.15/2.4
\textsuperscript{193} YB92/10.15/2.4
\textsuperscript{194} YB92/10.22/1.1–1.2
5.11 Dr Will published his report of the case, ‘Creutzfeldt-Jakob Disease in an Individual Occupationally Exposed to BSE’, as a letter in *The Lancet* on 6 March 1993. The letter concluded that ‘CJD in our case is most likely to have been a chance finding and a causal link with BSE is at most conjectural’. The letter noted that the only possible direct route of cross-contamination was that the farmer had drunk pooled milk from his herd which included that from the affected cow, but that epidemiological evidence had largely precluded milk as a route of transmission in spongiform encephalopathies.

5.12 This letter created much media interest over the following few days, and its contents were reported in *The Times*, *Today*, *Daily Express*, *Daily Mail*, and *Daily Telegraph* which also reported Mr Kevin Taylor (Assistant Chief Veterinary Officer, MAFF) stating ‘I don’t think that a link between this case and BSE is even conjectural’ and rejecting fears that the farmer might have contracted the illness from milk.

5.13 On 10 March 1993, Mr Jimmy Young of BBC Radio 2, interviewed microbiologist Professor Richard Lacey, who commented that:

> The good news is that this farmer, I think, got it too soon. If BSE produces this disease in people it will take, perhaps, another 5 or 10 years. So I think this is a one-off coincidence and I don’t think this farmer got his disease, CJD, from BSE. But nevertheless the underlying worries remain and I think it’s reasonable that this issue should be discussed.

5.14 The Second Annual Report of the CJDSU, published in July 1993, concluded that:

> This is most likely to have been a chance occurrence rather than indicating any causal link with BSE.

5.15 It further noted that:

> A farmer’s wife who was diagnosed in 1992 had worked on a small holding for over 20 years but there had not been a case of BSE in the herd (Wilesmith, Personal Communication).
‘The second farmer’ – July 1993

5.16 In early July 1993, Dr Will informed DH of a ‘second’ case of CJD in a farmer with BSE in his herd. The diagnosis had been confirmed by brain biopsy.\(^{204}\)

5.17 Dr Wight described the case in a minute sent on 12 July 1993 to the private secretaries to Baroness Cumberlege and Sir Kenneth Calman. The minute was copied to others in DH and to Mr Howard of MAFF. The 64-year-old dairy farmer from the West Country was thought to have had at least two BSE cases in his herd, which were diagnosed in 1992. He was also thought to have assisted in calving and to have drunk the milk from his herd. His clinical symptoms had begun in May 1993. She commented that the history did not suggest anything other than a sporadic case of CJD but that DH was taking expert advice on the case.\(^{205}\)

5.18 On 19 July 1993, Mr Kevin Taylor (MAFF) minuted the private secretary to Mrs Gillian Shephard, the MAFF Minister, in a response to a request for more detailed briefing.\(^{206}\) He noted that neither Dr Will nor the CJDSU intended to publicise the case at that time unless it attracted media attention, as they intended to include the information in their Third Annual Report due in approximately one year, ie, July 1994.

5.19 The minute attached a briefing note for the Minister. This specifically mentioned the consideration of occupational exposure to BSE as discussed in the CJDSU’s Second Annual Report which concluded that:

\[\ldots\] current information does not suggest that occupation is linked to an increased risk of developing CJD and it includes occupations which might involve an increased exposure to the agent of BSE.\(^{207}\)

5.20 On 20 July 1993, SEAC held a meeting to consider this ‘second case’.\(^{208}\) They decided that a connection between occupation and CJD was unlikely and no conclusions could be drawn from the available statistical information. A paper by Professor Smith was presented which concluded that ‘the observation of two cases in workers in dairy farms with BSE-infected herds is disquieting, but the evidence is insufficient at this stage to draw any definite conclusions’.\(^{209}\)

5.21 On 12 August 1993, the Daily Mail and Today publicised the story of the ‘second case’ of CJD in a dairy farmer.\(^{210}\) Both named the farmer and reported a DH spokesman saying that the Government’s experts had considered the case and ‘agreed that there are no features that give cause for undue concern’. The spokesman had also commented that it was most unlikely that there was any direct link between BSE and CJD in the patient.

5.22 In September 1993, the case study of this ‘second farmer’ was published in The Lancet. This letter gave the farmer’s age as 54.\(^{211}\)
5.23 At the next meeting of SEAC on 7 October 1993, the case was reconsidered. It was agreed that if a third case of CJD appeared in a farmer with BSE in his herd, a full Committee meeting would need to be convened. SEAC could not identify any further risk factors that a farmer might be exposed to, in general, and specifically with regard to the two cases, other than those previously considered.

5.24 In September 1994, the CJDSU published its Third Annual Report. This noted that case reports had been published on two dairy farmers with CJD who had had BSE in their herds. It indicated that a study of the occupations of CJD patients had provided no evidence that working with animals or animal products was associated with an increased risk of CJD.

First young suspect case of CJD (Case A) – January 1994

5.25 On 13 January 1994, an article in Today reported a case of brain disease in a 16-year-old girl, and claimed that she was the youngest victim of CJD. We refer to her in this chapter as case ‘A’.

5.26 The same day, Dr Roger Skinner (Principal Medical Officer, DH) minuted Dr Jeremy Metters (Deputy CMO, DH) informing him that Dr Will suspected that the case reported in the newspaper was one he had become aware of three months previously. Dr Will had said that the girl had an undiagnosed progressive degenerative brain disease and that it would be classified as a ‘possible’ case of CJD. The minute also noted that, if the case was definitely CJD, it would be the youngest case reported in the UK in the past 23 years. However, there had been cases of CJD in teenagers (one from the US, others from the rest of the world) from places where BSE is not found.

5.27 Dr Wight produced a note on 14 January 1994 for Dr Michael McGovern (Private Secretary to the CMO) and other DH officials. The note stated:

Points on this particular case

1. Diagnosis not confirmed. Clinically could be consistent with CJD, but EEG is not typical. Biopsy performed and shows spongiform change and astrogliaosis (as in CJD). Staining for abnormal prion protein is negative.

2. Duration of the disease so far about 1 year – longer than average (4 months). Aged 15 years at onset of illness. No family history of similar illness.

3. If diagnosis of CJD can be confirmed, this will be post-mortem on histopathological examination (but even this may not be definitive). Patient’s course static over last 3 months.

5.28 Under the heading ‘Age of Onset’ Dr Wight commented, ‘If confirmed as CJD, this is [the] youngest patient seen in the UK in 23 years (1970–93) since data...
[were] collected’. Her note had a separate heading for ‘Comparison with young onset cases in world literature’. Here she noted that Creutzfeldt’s first patient was 23 years old (reported in 1920), and that there were other cases of CJD in young people which predated the emergence of BSE. These were a 20-year-old female and a 16-year-old female in the US and a 19-year-old female in France. 219

5.29 On 26 January 1994, the Chief Medical Officer (CMO) released a statement in response to the media attention about this young CJD case. This stated that ‘no-one knows what illness she is suffering from’ and that ‘on the basis of the work done so far, there is no evidence whatever that BSE causes CJD’. 220

5.30 At its 16th meeting on 26 January 1994, SEAC considered information on Case A. 221 Dr Will presented the case saying the tests were inconclusive and that the case was possible CJD. Transmission studies were recommended should the patient be shown at post-mortem to have CJD. Additional information was discussed including that there was no history of human growth hormone, no family history, unpasteurised milk had been consumed by the patient, and she had worked in a cattery. It was subsequently confirmed that there had been no FSE cases locally and, specifically, none from this cattery.

5.31 At the same meeting, Dr Will informed the Committee that he had applied for MRC funding for transmission studies using the brain material from the two dairy farmers with CJD (see paragraphs 5.7–5.24). 222

5.32 On the evening of 26 January 1994, Channel 4 Television screened an episode of ‘Dispatches’ featuring the case of the 16-year-old girl (case A). As well as interviewing her family, the programme interviewed both Dr Gareth Roberts, a neuropathologist at St Mary’s Hospital, London, and Dr Tyrrell. On 15 April 1994 a report on Case A was published by the World Health Organisation. 223

‘The third farmer’ – December 1994

5.33 A ‘third case’ associated with farming where cattle in the herd had contracted BSE concerned a farm worker from Cornwall who had died in early December 1994, aged 54. There had been two confirmed cases of BSE on the farm, in August 1991 and October 1992. Additionally, a cow sold off the farm in December 1987 had been diagnosed with BSE in September 1988. 224

5.34 On 1 December 1994, the case was reported in the local newspaper, The Cornishman, while the patient was still in hospital. 225

5.35 On 19 December 1994, Mr Charles Lister, DH, minuted the private secretary to Baroness Cumberlege with information about this possible ‘third case in farmers/farm workers who have had BSE cases in their herds’. 226 This minute enclosed the article from The Cornishman and was copied to DH officials and to Mr Eddy at
MAFF. He noted that diagnosis would not be confirmed until post mortem, but the Surveillance Unit thought it highly likely to be CJD.

5.36 On the same day, Mr Thomas Eddy, MAFF secretary to SEAC, passed the newspaper article and basic information about the case on to MAFF Ministers and officials.\(^{227}\)

5.37 On 13 January 1995, SEAC held a special meeting to discuss the significance of this third case of CJD in a farmer in the first four years of surveillance.\(^{228}\) Dr Sheila Gore, an epidemiologist from the MRC Biostatistic Unit, was invited as an independent expert.

5.38 Detailed consideration was given to the case itself and the epidemiological implications. Dr Will commented that the post-mortem results were not yet available, but it was highly likely that the diagnosis of CJD would be confirmed. He stated that the man had no significant medical history and that he had worked as a farm labourer on the same dairy farm since 1955:

The man was known to have assisted with calving but never with any operative procedure; he rarely drank unpasteurised milk and never from BSE-affected animals. It was not known if he had ever eaten cattle feed.\(^{229}\)

5.39 As to the epidemiological significance of the case, the members recalled the advice given by Professor Smith after SEAC had considered the second case of CJD in a farmer:

Professor Smith had advised that if four cases arose in the first 5 years of the surveillance scheme the possibility of an association which was not due to chance had to be given very serious consideration.\(^{230}\)

5.40 Dr Gore commented that:

If the adult incidence of sporadic CJD in the UK was taken as one case per million (the figure used by Professor Smith) and if the same incidence applied to workers on dairy farms with BSE-affected herds, then the probability of observing three or more definite CJD cases in such workers in England and Wales in 5 years was low: 4 in 1,000. The probability was higher if the calculation was made using the total number of dairy farm workers in England and Wales. However, this was considered to be less relevant as the only reported cases of CJD in dairy farm workers since 1990 had been in lifetime dairy workers all with BSE-affected herds.

5.41 However, Dr Gore also said that the calculation of this probability had been based on the information to hand. She recommended that:

i. The number of dairy farmers should be put on a UK basis.

ii. It should be established whether the figure used for the proportion of herds with one or more cases of BSE applied to the UK or to England and Wales only.

\(^{227}\) YB94/12.19/3.1
\(^{228}\) YB95/1.13/1.1–1.4
\(^{229}\) YB95/1.13/1.1
\(^{230}\) YB95/1.13/1.2
iii. Actual CJD figures should be used for 1990 to 1994 rather than the guesstimate of one case per million.

5.42 The Committee concluded that the occurrence of CJD in three dairy farm workers, with BSE in their dairy herds, within the first five years of the surveillance study, was a matter of concern given the low probability of this happening by chance. However, there was no evidence to suggest that these were other than sporadic cases. The Committee expressed a wish for further information before making firmer conclusions, and recommended the following work to be undertaken as a matter of priority:

i. Further statistical analysis broken down by age, comparing the relative risks of developing CJD between farmers and other workers in contact with animals, and other occupational groups without such contact.

ii. Study of the working practices of risk occupation groups, eg, farmers’ contact with cattle feed dust.

iii. Incidence of CJD in UK farmers compared with countries with little or no BSE.

iv. Transmission studies with brain material from the third farmer.

5.43 It was concluded that the case did not require the Government to revise the measures taken to safeguard public health against occupational and other possible routes of exposure to BSE.

5.44 A draft DH statement was prepared to respond to any media enquiries. This confirmed that SEAC had considered the case to be a sporadic form of CJD. However, as this was the third case of a farmer with CJD, they wished to undertake further statistical analysis.

5.45 On 16 January 1995, Mr Eddy minuted the private secretary to the MAFF Minister, Mr William Waldegrave, outlining the discussion at the SEAC meeting and advising that MAFF was cooperating with DH in the further statistical analysis by providing information on the age distribution of farmers. The DH draft statement was also provided with this minute.

5.46 On 19 January 1995, Mr Lister sent a further note to the private secretaries for the CMO and Baroness Cumberlege advising that the post-mortem results were positive for CJD. The note also included previous advice from an epidemiologist that if four cases in farmers emerged within the first five years of surveillance the possibility of an association not due to chance must be given very serious consideration.

5.47 On 10 February 1995, SEAC discussed the case of the third farmer at their 18th Meeting. The minutes of the meeting record that Dr Tyrrell emphasised that transmission studies in mice and strain typing in mice of isolates from the three CJD cases in dairy farmers should be given the highest priority (see vol. 2: Science for an example of strain typing). This would involve brain material from the cases
being inoculated into the brains of mice and looking to see if the clinical features and neuropathology were similar to BSE in mice, therefore suggesting a link between BSE and these cases of CJD.

5.48 Dr Will provided preliminary information that this third case of CJD in a farmer did not have a mutation of the PrP gene. This excluded the case being familial CJD and suggested that the most likely diagnosis would be sporadic CJD. However, the patient was a codon 129 valine–valine homozygote, which was a less usual genotype for sporadic cases (see paragraph 4.29). Dr Will also indicated his wish to publish the details of this third case in a scientific journal.

5.49 Dr Will further commented on the likely clinical presentation if BSE was to transmit to humans via the oral route. He expected presentation to be as a cerebellar syndrome with ataxia, like that seen in peripherally induced iatrogenic CJD cases such as human growth hormone cases. The three dairy farmer cases were all typical of sporadic CJD, ie, a rapidly developing dementia.

5.50 The details of this third case in a dairy farmer were published in *The Lancet* on 30 September 1995 by the CJDSU. The farm worker had suffered a three-month history of forgetfulness, altered behaviour, slurring of speech, ataxia and myoclonus. There was marked cognitive impairment. The lack of a relevant medical history or family history of CJD and the information that the farmer was homozygous for valine at codon 129 of the prion protein gene were also reported.

**Second young suspect case of CJD (Case D) – May 1995 (later confirmed as vCJD)**

5.51 In the first quarter of 1995, two suspected cases of CJD in people under 50 were referred to the CJD Surveillance Unit. We shall call them ‘B’ and ‘C’. 241

5.52 A second suspect case of CJD in a teenager was identified in May 1995 when a brain biopsy, which provided no definite diagnosis on review, was referred for an opinion to the CJD Surveillance Unit. Dr Will told the Inquiry that despite the equivocal histology, attempts were made to obtain clinical information because of the remarkably young age of this patient. It was eventually established that there was no family history of dementing or ataxic illness and no history of exposure to human pituitary-derived hormone, neurosurgical procedures, or tissue grafting. We shall refer to this patient as ‘D’.

5.53 Dr James Ironside (CJDSU) gave oral evidence to the Inquiry about his examination of the biopsy. He recalled the brain biopsy material being sent to him by a colleague at the National Hospital of Neurology and Neurosurgery, London. He noted that microscopic assessment of the neuropathology showed ‘very little to suggest that this was in fact a case of CJD at all’. The features of spongiform change

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237 Ataxia – failure of muscle coordination
238 Myoclonus – muscle spasms
240 Ibid
241 Figure at S61D Will p. 8
242 Neither of these cases was finally confirmed as vCJD
243 S61 Will para. 37
244 S61 Will para. 37
246 T24 pp. 72–3
were not really present and there were none of the florid plaques or other features which were later to be associated with variant CJD. He added:

However, using the antibodies to PrP, using the immunocytochemical technique, there was a positive reaction and this was a finding that we had really not encountered before. I discussed this case with my colleague, Dr Bell, and we felt that the case could not be diagnosed definitively, but of course, since there was a positive reaction, that raised the possibility that this was a form of human prion disease, and that further investigations, as Dr Will suggests, were required. In particular, we wondered, in view of the age of the patient, and the somewhat unusual findings in the biopsy, if there was an underlying genetic abnormality that might explain this, because we were aware that in cases of familial CJD, the age of onset and the pathological features can often be unusual.247

5.54 Following the death of D on 21 May 1995, CJD was confirmed histopathologically by the hospital in Bath where he was treated.248

5.55 The 19th meeting of SEAC was held on 21 June 1995. Dr Will was unable to attend. There does not appear to have been any discussion of patient D or any other cases of CJD in young people.249

Third young suspect case of CJD (Case E) – August 1995 (later confirmed as vCJD)

5.56 Dr Will, in his statement to the Inquiry, noted:

A . . . young patient was referred to the Unit from another centre in August 1995 after a brain biopsy confirmed the diagnosis of CJD. Information on this case was obtained by the usual methodology. It is of note that young patients with CJD, including teenagers, had previously been identified in other countries in the past.250

5.57 We shall refer to this patient as ‘E’. Dr Will added that the cases of the patients we have designated ‘D’ and ‘E’ were published in letters to The Lancet in October 1995, and that plaques were described in reports of the neuropathology in these cases.

5.58 On 11 August 1995, Mr Lister minuted the private secretaries to Baroness Cumberlege and the CMO concerning the purposed 12 August broadcasting of a ‘World in Action’ programme about CJD in teenagers and dairy farm workers.251 This programme was to publicise the third case of CJD in a dairy farm worker and Mr Lister was concerned about the likely renewed press coverage of the area.

5.59 Dr Will received the histology report on a brain biopsy from case E on 1 September 1995.252 The report stated that:

247 T24 pp. 72–3
248 YB95/8.1/5.1 para. 5
249 YB95/6.21/2.1–2.8
250 S61 Will para. 37
251 YB95/8.11/2.1–2.4
252 S61D Will para. 9
The histology is that of a prion disease (spongiform encephalopathy). It is not possible to subclassify further this case on such a small cortical biopsy.

Dr Will wrote to Dr Ironside on the same day:

The crucial issue in this case is whether the pathological changes as reported are really typical for sporadic CJD . . . do you think that the appearances as described are similar to the plaques we sometimes see in the cortex of growth hormone recipients and would you accept their appearances as described as being within our normal experience for sporadic cases.

5.60 Dr Will stated in written evidence to the Inquiry:

I have no exact memory of the subsequent conversation, but I do recall that we had no reason to disagree with the pathology report and that it was not, at that stage, possible to say that the neuropathological changes were distinct from previous experience.

5.61 The 20th meeting of SEAC was held on 8 September 1995. The papers for the meeting included the fourth annual report of the CJD Surveillance Unit. This recorded at page 25:

Comment was made in the last Report regarding a case of suspect CJD in an adolescent. The diagnosis in this individual remains uncertain and may depend on eventual histological examination of the brain. It is unusual for patients with CJD to survive for longer than 12 months.

The diagnosis of CJD has recently been confirmed in a 19-year-old individual and detailed investigations are currently in progress (this case is not included in the overall analysis for this year’s annual report as the patient was identified after 30 April 1995). The occurrence of CJD in a patient of this age is exceptional but not without precedent (see Possible Creutzfeldt-Jakob Disease in an Adolescent, Weekly Epidemiological Record 1994, 15, 105–12). CJD has been described previously in two adolescents in the United States of America which is free of BSE and in one adolescent in France which was free of BSE at the time of the patient’s clinical illness. It would therefore be premature to conclude that the occurrence of CJD in an adolescent in the United Kingdom was indicative of transmission of BSE.

5.62 The teenagers mentioned in the Report were A and D above. At the meeting, SEAC were informed of a suspected case of CJD in a teenager (17 years old). This was case E. The minutes recorded:

. . . the pathology and clinical features of the patient, who remains in a coma, are atypical for CJD.

. . . It was the Committee’s view that the presentation of CJD in adolescents is exceptional but not without precedent. CJD has occurred in adolescents in other countries which are free from BSE and it would therefore be premature.
to conclude that its occurrence in a teenager in the UK was indicative of transmission of BSE.

5.63 On 29 September 1995, various newspapers reported the third case of CJD in a dairy farmer. Reference was made to a letter published in The Lancet (dated 30 September 1995) by Dr (now Professor) Smith (LSHTM).

5.64 The letter reported:

The occurrence of CJD in another dairy farmer with a potential occupational exposure to BSE is clearly a matter of concern. Statistical analysis indicates that the probability of discovering three or more dairy farmers with CJD by chance since 1990 in England and Wales ranges from 0.09 to 0.0002, depending on the occupational denominator (individuals who work on farms to full-time workers on BSE-affected dairy farms).

5.65 Statistics for CJD in European farmers were also reported in the 30 September 1995 edition of The Lancet. The paper concluded that ‘there is no differential increase in the risk of CJD to farmers in the UK through potential occupational contact with cases of BSE’. On the continent there was also a slightly higher proportion of cases of CJD arising in farmers. This indicated that in the UK, CJD in farmers had probably not arisen from transmission of BSE.

The fourth farmer – September 1995

5.66 On 28 September 1995, Dr Wright minuted the private secretary to the CMO about a probable fourth case of CJD in a farmer. The 59-year-old beef farmer lived in North Wales and was alive when the case was reported to the CMO. The farm, which had a 70-strong suckler herd, had a confirmed case of BSE about four years previously in a 4½ to 5-year-old cow.

5.67 The minute recorded the urgency of dealing with the issue as the case was in the public domain and BBC Wales were making a programme referring to the case. An urgent meeting of SEAC was called for the following week.

5.68 On 4 October 1995, SEAC held a special meeting to discuss this further suspected case of CJD in a cattle farmer. Professor Smith (LSHTM) and Dr Cousens (LSHTM) were in attendance to provide the Committee with expert epidemiological advice.

5.69 Dr Will advised that although the Unit had initially clarified the case as probable CJD, he felt that it was more appropriate to look at it as a suspect case. Consideration was given by SEAC to European data that showed 12 cases of BSE in France, along with a progressive neurological disease in a farmer associated with
one of those cases. (In the eventuality, this farmer was not diagnosed with CJD. At the beginning of January 2000, there had been no reported cases of CJD in farmers in France where BSE had been found in that farmer’s herd.)

5.70 Mr Wilesmith gave SEAC information about the farm associated with the possible UK fourth case of CJD under discussion. The farm had not been visited by MAFF. It had one case of BSE in a purchased animal which died in September 1991. From available information, the animals had not been fed on concentrates (although this had not been double-checked). It was thought, however, that the farm did have a big poultry battery unit, which may have meant that ruminant-derived feed was available on the farm.

5.71 Dr Cousens made a presentation of the epidemiology. He had calculated age specific mortality rates for sporadic CJD from 1990 to 1994 and applied these to data on farmers to calculate the expected number of sporadic CJD cases in farmers. The following conclusions were reached:

i. there had been an alarming number of cases in farmers who had had contact with cattle with BSE. However, other occupational groups, expected to carry greater risk (eg, abattoir workers, veterinary surgeons), did not appear to be affected;

ii. it was now difficult to explain the cases as a chance phenomenon. Yet the absolute risk still remained extremely low;

iii. it was unclear whether the possible risk factor might be associated with cattle with BSE or the food given to them; and

iv. as there was a problem with establishing a causal link, transmission studies would be extremely important.

5.72 At this meeting, Dr Wight invited members of SEAC to make a fairly clear statement on how they viewed the significance of a fourth case and to consider whether they were satisfied that nothing else needed to be done in terms of practical measures. In evidence to the Inquiry, Dr Wight said that trying to get a clear statement as to what would be a significant number of cases in farmers was bound to be difficult. She said, ‘I do not think that SEAC any more than anybody else had any idea how to make sense of this at this stage.’ At the meeting, Dr Tyrrell’s response was that although numbers were higher than expected, they were still extremely small. It would be irrational to take specific measures at the moment. Members of SEAC agreed to draw up a statement which the Department of Health could issue in response to media inquiries. The text of the statement included the following:

The Committee concluded that it was difficult to explain this simply as a chance phenomenon. There is a statistical excess in cattle farmers compared with the general population but the absolute risk, even for farmers, is extremely low at about 2 cases per million per year. There may be other explanations for such an association besides infection with BSE, and the Committee noted that there are no recorded cases in other occupational
groups such as veterinarians who might be expected to be similarly exposed. They also noted that the surveillance of CJD elsewhere in Europe has shown a similar incidence of CJD in farmers, including dairy farmers, in countries with no or very few cases of BSE. They therefore felt that it was important to undertake further epidemiological studies to detect any particular risk factors which might be involved, and reiterated their advice that the UK cases of CJD in cattle farmers and the strain of agent recovered from them should be studied in detail.

The Committee have asked for further work to be done, but have not altered their advice to Government on the precautions necessary to protect either the public health, including farmers, and animal health.

5.73 Mr Eddy minuted the MAFF Minister and Parliamentary Secretaries advising them of the outcome of the SEAC meeting. He commented that SEAC had concluded that it would be worrying if the fourth case of CJD in a farmer from a BSE farm was confirmed.

The chances of four CJD cases occurring randomly in farmers with BSE in their herds was . . . [since 1990] around 3/10,000. The Committee therefore concluded that it was difficult to explain the incidence as a chance phenomenon. This is a change to the Committee’s position; it had said that the most likely explanation of the three previous cases of CJD in dairy farm workers was that they were chance phenomena.

5.74 Mr Eddy also stated that the SEAC did not recommend changes to any of the measures currently in place to protect human and animal health, including those of farmers and others handling cattle and BSE suspects.

5.75 On the same day, Mr Eddy prepared a second minute which was sent to Dr Matthews and Mr Keith Meldrum (CVO) amongst others about discussions during the SEAC meeting. Mr Eddy included a list of four ways in which the farmers might have been exposed to BSE that might have then led to their infection with CJD:

i. cattle were excreting the agent in some form – no evidence for this;

ii. meat and bone meal (MBM) in cattle feed – if so this would affect pig and poultry farmers equally (these feeds also contained MBM);

iii. normal food – unclear why this discriminated in favour of farmers, although farmers could have been exposed to foods that other people might not have been routinely exposed to, such as unpasteurised milk; and

iv. contact with animals – possibly animals killed on the farm.

5.76 These four possible routes of infection had been discussed at the SEAC meeting but it was agreed that none of these routes were particularly plausible.
Evolution of knowledge leading to the identification of new variant CJD and the hypothesis of causal link with BSE between late 1995 and early March 1996

5.77 During the quarter to 30 September 1995 four further cases of CJD in people under the age of 50 had been referred to the CJDSU.\textsuperscript{272} We will refer to them as F, G, H and I.\textsuperscript{273} A further seven cases were to be referred in the quarter to 31 December 1995. We refer to them as J, K, L, M, N, O and P.

5.78 At SEAC’s special 21st meeting of 4 October 1995, Dr Will summarised recent sporadic cases of CJD in young people. There were currently two cases in teenagers, a 19-year-old and a 17-year-old. The case in the 17-year-old had unusual pathology, although this could be related to age. There were also other cases in their 30s and 40s, which was unusual. However, although this was a change from usual experience, it was difficult to relate to BSE.\textsuperscript{274} The 19-year-old and 17-year-old were cases D and E respectively. Dr Will has informed the Inquiry that the other cases he had in mind were F, G and H.

5.79 One of the cases referred in the December quarter was J. This patient, aged 29, was referred to the CJDSU after a brain biopsy at another hospital.\textsuperscript{275} Following a review of the biopsy results for this case on 18 October 1995, Dr Will noted that one of the neuropathological features common to all three cases (D, E, and J), was plaque deposition. He considered that these three cases were unusual, because only about 10 per cent of cases of sporadic CJD had plaque deposition. However, he did not consider that there was sufficient evidence to identify these three cases as neuropathologically distinct at that stage.\textsuperscript{276} Further information on the formation of plaques is given in vol. 2: Science.

5.80 On 26 October 1995, Mr Lister (DH) minuted the Private Secretary to Baroness Cumberlege, with copies to the CMO and other DH officials, as well as Mr Render at MAFF.\textsuperscript{277} This minute enclosed proof copies of letters which were to be published in The Lancet the following day. The letters concerned the cases of D and E. He noted that the 17-year-old whom the press first alleged had CJD nearly two years previously was still in a coma and the cause of her illness remained uncertain. This was case A. Mr Lister added that the CJD Surveillance Unit was investigating a confirmed case of CJD in a 29-year-old from London. The patient was still alive, and the diagnosis had been confirmed by brain biopsy. The patient in question was J.\textsuperscript{278} Mr Lister’s minute also noted a probable case of CJD in a 38-year-old woman which had attracted media attention. This case was G.\textsuperscript{279}

5.81 On 28 October 1995, cases D and E (the two suspect CJD cases in teenagers described earlier) were reported in The Lancet. The case report for E indicated that the diagnosis had been confirmed by brain biopsy and was entitled ‘Sporadic CJD in a 16-year-old in the UK’. It continued:

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\textsuperscript{272} Figure at S61 Will p. 8
\textsuperscript{273} G was later excluded from the figures in March 1996, when a prion protein gene mutation was identified, establishing that this was the cause of the disease
\textsuperscript{274} YB95/10.4.1--4.2, para. 7
\textsuperscript{275} S61 Will para. 38; S61D Will para. 11
\textsuperscript{276} S61D Will para. 12
\textsuperscript{277} YB95/10.26/1/5
\textsuperscript{278} This case appears to have been mistakenly referred to within MAFF as a case in a 28-year-old man (YB95/10.26/3.1). Professor Will has explained to the Inquiry that no male aged 28 years was referred to the CJDSU at this time, and since the age of onset of clinical symptoms in case J was 28 years, the minute may have mistaken a male for a female case
\textsuperscript{279} Case G was later found to have a prion gene mutation
A 16-year-old girl was first seen in September 1994. In March 1994, she injured her right foot during a fall and subsequently developed right-sided lower lumbar backache and numbness in the fingertips and face. In August 1994, she developed slurred speech, poor balance, clumsiness of her limbs, and urinary frequency.\textsuperscript{280}

5.82 The report on D also referred to sporadic CJD in the title and stated:

An 18-year-old male was initially referred to a psychiatrist with suspected depression. He gave a 6 month history of deterioration of memory, complaining that he had ‘gone nutty’ . . . There was no family history of dementing or ataxic illness and no history of exposure to human pituitary-derived hormone, neurosurgical procedures, or tissue grafting. For a period of 8 years he visited his aunt’s farm annually and would have drunk unpasteurised milk and been exposed to cows. No cases of bovine spongiform encephalopathy (BSE) have been reported in this herd.\textsuperscript{281}

5.83 The report on D concluded ‘However, it is unlikely that CJD and particularly cases with a typical clinical presentation and histology would have been previously missed in teenagers.’\textsuperscript{282}

5.84 An update on the CJD situation was listed as agenda item 7 for SEAC’s 22nd meeting on 23 November 1995. This was not reached because of lack of time.\textsuperscript{283}

5.85 In late 1995, Dr Will and others at the CJDSU considered the possibility that the identification of these three confirmed young cases of CJD (D, E and J) might be due to ascertainment bias:

In 1994, the incidence of CJD in England and Wales was double that of earlier study periods, including the period 1980–84, during which a similar prospective surveillance study of CJD, using similar methodology, had been undertaken (see 4th Annual Report of the CJDSU). This rise in incidence was judged to be ‘most likely related to improved ascertainment of cases’ and that ‘. . . the major influence on the increased incidence of cases is an increased number of cases of CJD in those aged 75 and over . . .’. There was a possibility that a similar bias in ascertainment may have occurred in younger age groups.\textsuperscript{284}

5.86 Also in late 1995, Dr Will considered the possibility that young cases of CJD might in the past have been misclassified as subacute sclerosing panencephalitis (SSPE) – a chronic progressive illness seen in children a few years after measles infection and usually considered a slow virus disease. The possibility of misdiagnosis of such cases as SSPE had been raised by a survey of SSPE in Poland, in which three young cases of CJD, including one teenager, had been identified. On 19 December, in the light of this possibility, Dr Will reviewed the SSPE register held by the PHLS to identify any cases of suspect SSPE, not subsequently

\begin{itemize}
\item S61D Will para. 8
\item YB95/11.23/1.1atf.13; SEAC 22
\item S61D Will para. 13
\end{itemize}
confirmed, that might have a phenotype compatible with CJD. No such cases were identified.285

5.87 In written evidence to the Inquiry, Dr Will listed other factors that were influencing his views in late 1995:

The post-mortem rate in suspect cases of CJD since 1990 had increased from approximately 50 per cent [of suspect cases] in the 1980–84 study to over 70 per cent from 1990 and there was, therefore, an increased chance of identifying atypical cases.

Through a review of all cases of suspect CJD since 1970, in which an alternative diagnosis had been confirmed neuropathologically, a case aged 16 years from 1980 was identified. This case had originally been identified as CJD after neuropathological examination, but this diagnosis was later retracted, perhaps because CJD was thought to be an unlikely diagnosis in a patient in this age group.

The hospital notes of one of the three young cases identified in the UK in 1995 included the statement ‘First slides of the biopsy do not suggest any striking diagnosis – await more specific stains’. The diagnosis of CJD was supported by slides stained immunocytochemically for PrP, a technique developed in the 1990s and not available in previous study periods. This may have improved case ascertainment in the 1990s and this led us to re-examining and immunostaining tissues from past cases of CJD in the younger age groups.286

The hospital notes referred to were those for case J.

5.88 In his evidence to the Inquiry, Dr Will noted that by 14 December 1995 ten suspect cases of CJD in patients aged less than 50 years had been referred to the CJDSU (cases D, E, F, G, H, J, K, L, M and O).287 He also noted that by 31 December 1995 only three of these cases had been confirmed neuropathologically as CJD (cases D, E and J), but none had been classified as new variant CJD because the clinicopathological phenotype had not been recognised at that time. He cautioned that it was important to note that some of these ten suspect cases were not finally confirmed as cases of new variant CJD. Dr Will has also informed the Inquiry that on 15 December 1995 a further case in an individual under 50 was referred to the CJDSU after a neuropathologist diagnosed GSS. This was Case P.288

5.89 A further three referrals of suspect CJD cases aged less than 50 years were made in the period from January to 20 March 1996. We refer to these cases as Q,R and S. Dr Will explained in a statement to the Inquiry that during this time there were two main issues, with sub-issues, that needed consideration in order to assess the significance of the cases:

285 S61D Will para. 14
286 S61D Will para. 15
287 S61D Will para. 16. Dr Will has explained to the Inquiry that these were not the only referred cases aged less than 50. The cases identified in the text were those which the CJDSU had placed on its list of ‘young suspect cases’
288 Dr Will has told the Inquiry that this case was not regarded as a young suspect case of sporadic CJD but as a case of familial prion disease on the basis of neuropathology. A genetic mutation was identified in August 1996 confirming that this was a case of an hereditary form of human prion disease
i. To what extent are these cases different and new?
   a. is there a novel clinical phenotype?
   b. is there a novel neuropathological phenotype?
   c. are these cases linked to mutations [in the prion genes]?
   d. is there ascertainment bias or increased efficiency of surveillance?

ii. To what extent might these cases be linked to BSE?
   a. are these cases in the UK distinct from previous experience?
   b. are these cases only occurring in the UK?

5.90 When asked about this during his oral evidence to the Inquiry, he confirmed that affirmative answers to points (i.) (a) and (b) would suggest that cases were ‘different and new’. Conversely, if (i.) (c) and (d) were true, it would suggest cases were due to factors that had been around in the past, eg, cases linked to prion gene mutations.

5.91 We set out below how Dr Will’s assessment of these issues changed from early January to 20 March 1996, and how by 8 March he and Dr Ironside concluded they had sufficient evidence to be confident that they had identified and characterised a new variant of CJD. Later in March, it became apparent that this new variant was restricted to the UK, consistent with a causal link to BSE.

5.92 On 4 January 1996, the diagnosis of CJD was confirmed by neuropathology in two more of the ten suspect cases identified in paragraph 5.89 above. These were patients K (aged 29 years at death) and H (aged 30 years at death). The histological appearances were judged to be unusual by the CJDSU and extensive plaque deposition was detected. The possibility of a genetic form of human prion disease was raised in these cases as they featured plaque formation, a feature in some cases of hereditary prion disease.

5.93 Dr Will updated SEAC on CJD surveillance results at their 23rd meeting on 5 January 1996. He ‘reaffirmed that the incidence of CJD in dairy farmers in Europe showed an excess over the incidence for the population as a whole’. He confirmed that a 52-year-old abattoir worker from York was suspected of having CJD. The patient had worked mainly as a stockman in a mixed abattoir for 18 months in the late 1980s, and had occasionally pithed animals but had much less exposure than other abattoir workers. Dr Will believed that the patient was no more than a suspect at that stage.

5.94 The minutes of the meeting record that Professor Smith commented on this case:

   He [Professor Smith] felt that it was not possible to come to any conclusions on the basis of this case alone even if CJD is confirmed. Nevertheless, taking into consideration the affected farmers as well, and even though the abattoir worker was in an apparently relatively low risk category, the ‘box’ of ‘at
risk’ occupations was getting full compared to expectation on pure chance and could not be dismissed.293

5.95 At this meeting, Dr Will also reviewed the age distribution of cases at the meeting. He continued to have no concern about the incidence of disease in those aged over 30 but the number of cases under 30 was worrying. He then went on to list the four definite and one possible case under 30.294 The definite cases were D, E, J and K. The possible case, a 29-year-old who was still alive, was L.

5.96 Dr Will told SEAC that there were two confirmed cases in patients between 30 and 40 years old. The minutes record that Dr Will also mentioned ‘a 35-year-old suspect, who now looks unlike CJD’.295 The two confirmed cases were H and G, while the 35-year-old suspect was O.

5.97 The minutes noted that although Dr Will was not ‘unduly concerned at the overall number of CJD suspect cases that had occurred in the under-30 age bracket, what he did find worrying was that all cases had occurred over a very short period’.296 Dr Will has added in written evidence to the Inquiry that he is confident that there was a more extended discussion than that recorded and that this included ‘some of the caveats to the interpretation of the data available 5.1.1996’.297

5.98 By the time of the SEAC meeting on 5 January there had been 14 referrals of suspect cases of CJD in patients under 50 years of age to the CJDSU.298 Diagnosis of CJD had been confirmed in four of these cases at death (cases, D, H, K and G) and by biopsy in two cases (E and J).299 In his statement, Dr Will considered that by 5 January 1996, the scientific criteria on which these cases could be judged to be significant were fulfilled as follows:

i.

a. is there a novel clinical phenotype?: not identified;

b. is there a novel pathological phenotype?: not identified;

c. are these cases linked to PRNP mutation?: no mutation identified in three cases;

d. is there ascertainment bias or increased efficiency of surveillance?: probable;

ii.

a. are these cases in the UK distinct from previous experience?: not identified;

b. are these cases only occurring in the UK?: unknown.

5.99 We now turn to developments at the CJDSU during January 1996 leading up to the identification later that month of a possible novel clinical and pathological phenotype in some confirmed CJD cases in patients under 50 years of age.

293 YB96/1 5/1 6–1.7
294 YB96/1.5/1.7
295 YB96/1.5/1.7
296 YB96/1.5/1.8
297 S61D Will para. 20
298 As indicated earlier, these were not the only referred cases under 50 years of age. The 14th case was later classified as a hereditary form of human prion disease
299 YB96/1.5/1.7
5.100 On 8 January 1996, the CJDSU confirmed the diagnosis, by neuropathology, of CJD in two further cases (cases L and M) bringing the total number of confirmed cases to eight – comprising cases D, E, G, H, J, K, L and M. Dr Will wrote to the clinicians responsible for the two latest patients noting the possibility of a genetic form of CJD as the histological appearances were unusual for sporadic CJD. He also commented on the importance of genetic analysis in these cases.\(^{300}\)

5.101 In early 1996, Dr Will contacted Professor Hofman, who coordinated the European surveillance project on CJD, to request information from participating countries on young cases of CJD, amongst other things.\(^{301}\) The CJDSU received this information later in January. The information showed that from 1993 to 1 February 1996 there were five deaths from sporadic CJD in continental Europe in the age range 20 to 39. Dr Will told us that ‘this data indicated that the age distribution of young sporadic CJD in continental Europe was similar to the age distribution of young cases in the UK, with the exception of the two cases in teenagers’.\(^{302}\) When Dr Will gave oral evidence, he qualified this statement:

There is an important qualification, and that is in the European surveillance system we are talking about a relatively and much larger population than the UK and a more prolonged study period in which these cases have been identified. So the comparison is not exact and we have to be aware of that. The only point I was trying to make is we did at that stage know that there were cases in the younger age group which had been identified in the European surveillance system, although I must stress not in teenagers at the time.\(^{303}\)

5.102 Towards the end of January, Dr Will and Dr Ironside were becoming increasingly concerned about the number of cases of CJD in the younger age groups and the short time period in which the cases had been identified. Dr Will told us:

Concern about the presence of plaques on neuropathological examination in all the confirmed cases to date was heightened by previous work from the unit, which had indicated a significant excess of plaques in association with a valine or heterozygous [prion protein] genotype. At this stage we were aware that three of the young cases were methionine homozygotes and that these were not associated with [prion protein] mutations.\(^{304}\)

5.103 Summary tables were produced by Dr Martin Zeidler of the CJDSU on 16 and 29 January 1996, on the clinical, investigative and pathological data on suspect or confirmed cases aged less than 50 years.\(^{305}\) The results from these tables are shown at Annex 2. Dr Will told us that around this time:

. . . (neither my colleagues nor I can recall the exact date) by the examination of summarised clinical and pathological data we identified what we believed might be a common clinical phenotype, which was linked to plaque deposition neuropathologically. This phenotype included, in addition to young age at death, a relatively prolonged duration of illness in relation to
sporadic CJD, early psychiatric symptoms, prominent ataxia and the absence of the characteristic EEG appearance seen in sporadic CJD . . . 306

It is important to stress that the identification of this ‘novel’ phenotype was tentative at this stage. Each component of the phenotype can occur in sporadic CJD. Some of the cases on which the putative phenotype was based were suspect and at that stage unconfirmed and one of these cases was subsequently discovered to have an insert mutation of [the prion protein gene]. There was the possibility that the cases had a heterogeneous aetiology, with some cases sporadic and some genetic. The latter issue was the subject of intense discussion, which continued over subsequent weeks. We believed that genetic analysis was essential to determine whether some of the cases were mutation-associated . . . 307

[The] review of historical data on the clinical phenotype of young cases of CJD led to the identification of some cases with a similar phenotype to that proposed in the recent young cases. For example, in the 1970–79 study of CJD the following cases of sporadic CJD were identified:

- A patient aged 34 years presenting with depression and seen by a psychiatrist. Total illness duration 8 months. EEG typical.
- A patient aged 35 years presenting with emotional lability and who developed ataxia. Total illness duration 23 months. EEG showed slow activity.
- A patient aged 28 years presenting with depression and seen by a psychiatrist. Total illness duration 22 months. EEG showed some triphasic complexes. 308

5.104 Dr Will explained, in written evidence to the Inquiry, the views he held at the end of January 1996:

I had become increasingly concerned about the young cases of CJD, but there was insufficient scientific evidence to reach a conclusion about the novelty of these cases, nor to reach a judgement about whether these cases might be causally linked to BSE. The interpretation of the neuropathological findings was of critical importance and I asked Dr Ironside for his opinion. Dr Ironside said that there clearly were very unusual pathological features in these cases, but that it would be premature to conclude that these cases were linked to BSE on the basis of the neuropathological findings alone.

5.105 Reflecting these developments, Dr Will set out in written evidence his assessment as of 1 February 1996 of the extent to which some of the scientific criteria were met. We describe this below, and give a comparison for each criterion where the position had changed since 5 January:

i.

a. is there a novel clinical phenotype?: possible (compared with ‘not identified’ on 5 January);
b. is there a novel pathological phenotype?: possible (compared with ‘not identified’ on 5 January);

c. are these cases linked to PRNP mutations?: no mutation identified in three cases;

d. is there ascertainment bias or increased efficiency of surveillance?: probable;

ii.

a. are these cases in the UK distinct from previous experience?: possible (compared with ‘not identified’ on 5 January);

b. are these cases only occurring in the UK?: unknown.

5.106 At the 24th meeting of SEAC on 1 February 1996, Dr Will reported on the CJDSU findings in the young cases of CJD. By this time, five cases [cases D, E, J, K, L] of CJD under the age of 30 had been confirmed by neuropathology, three of whom were dead [D, K, L] and two alive [E, J]. However, genetic screening for mutations was incomplete, so familial CJD could not be ruled out. He also referred to two cases of confirmed CJD in the 30–39-year-old age bracket [cases H and G] bringing the total to seven cases confirmed in patients under 40 years of age. In addition, he referred to a further patient P who was in the 30–39 age group with a pathology suggestive of Gerstmann-Sträussler Syndrome (GSS) and a further confirmed case of CJD in a 41-year-old [case M]. The minutes of the meeting record:

In all of the cases mentioned above (except the GSS case and the one case where results are incomplete) there was extensive plaque formation in the cerebral cortex, cerebellum and spinal cord. An extensive and unusual pattern of PrP deposition was an unexpected finding. Dr Will reported Dr Ironside’s view that it is premature to decide that these cases are linked with BSE. Cerebellar and spinal cord plaques are evident in hGH cases.

5.107 In written evidence to the Inquiry, Dr Will clarified what was known at that time about the neuropathology of the cases:

I am recorded as saying in paragraph 21 [of the minutes of the SEAC meeting] that ‘In all of the cases mentioned above there was extensive plaque formation in the cerebral cortex, cerebellum and spinal cord.’ I regret that I had not previously recognised that this statement is inaccurate and I cannot recall whether the error is in what I said or what I am recorded to have said. By 1.2.1996, seven cases of what was subsequently recognised as new variant CJD had been confirmed neuropathologically. In two of these cases the neuropathological confirmation was by brain biopsy and, at that stage, information on regional neuropathology, including spinal cord, cannot have been available. With the assistance of the neuropathology staff at CJDSU I have identified that on 1.2.1996 full regional neuropathology was available.
in three cases and minimal regional data, excluding spinal cord, was available in a further two cases, although at that stage the neuropathological phenotype of nvCJD had not be identified.\textsuperscript{312}

**5.108** The minutes of SEAC’s 24th meeting also record that:

> Dr Will reiterated that the crucial issue is not simply the young age or pathology of recent cases but the short time scale in which five cases in individuals under 30 years of age had occurred. The dates of onset of symptoms of the cases were February 94, May 94, June 94, January 95 and April 95 although they were not reported to the CSU in that order. He advised SEAC that definitive genetic data on these five cases would soon be available and that he intended to publish the clinico/pathological data together with that of cases under 40 years of age. Details of the third young case will also soon be published. Dr Will agreed to let SEAC see an agreed proof copy of the paper. This would not be for amendment by SEAC and must remain confidential. It was agreed that a statement from SEAC should be prepared before the paper was published.\textsuperscript{313}

**5.109** In written evidence to the Inquiry, Dr Will expanded on the discussions at the meeting in relation to this:

> In my view it was essential that the descriptive information on these cases was published, although this would almost certainly not have been possible until the genetic data was available. The short time scale in which five young cases of CJD aged less that 30 years had been identified was clearly a matter of concern, but I did not at that time believe there was sufficient clinical, pathological or epidemiological evidence to indicate that we had identified a novel clinicopathological phenotype of CJD. The reasons for this view are indicated above and included the possibility of ascertainment bias, the data on young cases identified in continental Europe and concerns about improvement in neuropathological diagnosis following the introduction of modern [biochemical] techniques. Although not minuted, I believe that some of these issues were discussed at SEAC.\textsuperscript{314}

**5.110** The minutes also record that, Professor (now Sir) John Pattison, Chairman of SEAC, concluded that:

> The unusual data on young cases is of greater concern than the cases in farmers which appeared to be classical sporadic cases with typical pathology. He repeated the need to look at young people in other countries. If these patients shared the unusual pathology it would be comforting. It could be that CJD in young cases was different because of the age of the patient.\textsuperscript{315}

**5.111** At the meeting Dr Will emphasised the urgency of strain typing of these cases of CJD.\textsuperscript{316} In written evidence Dr Will expanded on his reasons:
. . . I had been concerned since the early years of the project that the identification of small numbers of atypical cases of CJD might be very difficult to interpret from an epidemiological perspective, particularly if there were ascertainment bias in comparison to previous study periods. It was, in my view, essential to obtain information from laboratory strain typing studies on these young cases as this might be crucial to an evaluation of whether or not these cases were linked to BSE.\[317\]

5.112 In oral evidence he added:

What I am really saying there is it is extraordinarily difficult to assess small numbers of cases when you are carrying out a national surveillance project. It is a very difficult thing to do. Therefore, the issue of having further scientific evidence in relation to these cases was critically important. And if I may say, in the end it was critically important in providing very strong evidence that links BSE to the occurrence of new variant CJD.\[318\]

5.113 The minutes of the SEAC meeting also record that Dr Will described recent developments in relation to sporadic CJD:

. . . Recent findings suggested that there are two subsets of sporadic CJD: those with an extended duration of illness with plaques in the spinal cord and cerebellum and those with a short duration of illness which do not show such plaques. Dr Will said there were no apparent environmental factors identified, except that 5 of the 9 spinal cord positive cases had had abdominal surgery, in three cases in the 1950s/60s. None of the spinal cord negative cases had had abdominal surgery.\[319\]

5.114 In written evidence Dr Will explained why he had presented this information:

In paragraph 21 [of the SEAC minutes] reference is made to a description I gave of two subsets of sporadic CJD, differentiated by the presence or absence of PrP staining in the spinal cord. The reason I presented this data was in order to ensure that SEAC were fully informed about recent developments that might be of concern. It is important [to] stress that this data on spinal cord neuropathology related to sporadic CJD and not new variant CJD.\[320\]

5.115 Dr Will emphasised this point at his oral hearing:

Just to be completely clear about this, this is nothing to do with new variant CJD. And the reason it was presented was because I felt, at the meeting, that SEAC should have access to all the information that we had that might be a cause for concern.\[321\]
Results of statistical analysis of CJD in young cases

5.116 On 5 February 1996, Dr Sheila Gore (MRC Biostatistics Unit in Cambridge) wrote to Dr Will about the results of her statistical analysis of CJD incidence. Her letter (written on the basis of information supplied at a time when four sporadic CJD cases had been diagnosed in individuals aged under 40) included the following:

Thank you very much for the data on age and farming occupation of sporadic CJD cases diagnosed in the UK in the 5 year period 1985–89. Since about 21 million persons in UK are aged 15–39 years, the three sporadic CJD cases (aged 35, 36, 38) diagnosed under 40 in 1985–89 give an estimated sporadic CJD incidence of 0.0286 per million person-years in this age group. Since 1 May 1990, the four sporadic CJD cases diagnosed under 40 (two teenagers, 29, 30) may be compared to 3.6 expected in six years \([0.0286*6*21=3.6]\) based on the 1985–89 cases and the probabilities of observing 4 or more cases \{also 5+, 6+, 7+, 8+, 9 or more\} are 0.48 \{0.29, 0.16, 0.07, 0.03, 0.012\} in the context of this expectation.

Please note that I have taken no formal account of the fact that the four 1990s cases are younger than the three 1985–89 cases. Nonetheless, the newly available age-specific UK data for 1985–89 are somewhat reassuring that 4 cases diagnosed under age 40 since 1 May 1990 are not out of line with expectation based on the earlier quinquennium. It would be further reassuring if data were adduced from your EC collaboration as follows: number of persons in country aged 15–29 and aged 30–39, number of months of active CJD surveillance, number and ages of sporadic CJD cases diagnosed at ages under 40 during those months.

5.117 After commenting on data on farming occupation, Dr Gore concluded:

. . . Thus the 1985–89 farming occupational cases accord with the 1990s estimated age-appropriate sporadic CJD incidence for this occupational group as derived from UK-wide age-specific incidences of sporadic CJD.

Dr Will’s presentation at the Parliamentary Food and Health Forum on 20 February 1996

5.118 On 20 February 1996, Dr Will made a presentation at a meeting called by the Parliamentary Food and Health Forum to discuss the relationship between BSE and CJD. Dr Dealler, a medical microbiologist, was the other invited speaker at the meeting. In evidence to the Inquiry Dr Will set out an assessment, as at the date of this meeting, of the extent to which the scientific criteria had been met (in relation to judging the significance of the cases). This assessment did not differ from his assessment of 1 February (see above).
The report of the meeting recorded that:

Dr Will opened by saying that the theoretical risk of BSE to the human population was judged to be remote by the Southwood Committee in 1989, and this view was supported by the World Health Organisation, the European Community and other organisations. Although the cause of sporadic Creutzfeldt-Jakob Disease (CJD) was not known, the available evidence virtually precluded scrapie in sheep as a source of human disease. Dr Will said there was, however, a theoretical possibility that the BSE agent might be more pathogenic to man than was scrapie, and a series of legislative measures have been taken to minimise any potential risk to the human population in the UK. He said that current evidence did not suggest any definite change in the pattern of CJD that could be attributable to BSE, but it would be many years before such a change could finally be excluded . . .

Dr Will explained that there had been a slight increase in CJD in the 1970s, which levelled off only to increase again in the 1990s. Evidence suggests that this increase may have been due to improved ascertainment in the elderly. Parallel surveillance of CJD has also been taking place in the European Union and, in the period 1993–94, the incidence had been similar to that in the UK. This surveillance had shown no change in CJD which could be attributed to BSE.

Dr Will went on to say that there was no overall change in the age-specific incidence of CJD in the UK, and that the incidence of CJD amongst farmers showed no mechanism for the transference of BSE. He added that it was difficult to conclude what was happening amongst diary farmers, and that research was underway.

Dr Will said that while current information was reassuring, any risk to man from BSE might not be evident for some years, although there was currently no proof of a link between CJD and BSE.

Dr Will’s comments on an MLC briefing paper on 23 February 1996

On 12 February 1996, Mr Mike Skinner of DH (Health Aspects of the Environment and Food Division) sent an MLC briefing paper on BSE to Dr Will, Professor Pattison and Professor Collinge, and requested their views on it. The paper had been sent by Mr Don Curry (Chairman of the MLC) to Dr Eileen Rubery of DH on 3 January. The briefing paper stated:

British beef is safe to eat. The existence of BSE in cattle and the similar disease in humans, CJD (Creutzfeldt Jakob Disease) does not imply any link between the two . . .

The most eminent scientists who are involved in studying and seeking to understand the disease do not believe that there is a significant risk to humans. They include: Professor John Pattison, Dean of University College
Medical School and Chairman of the independent Spongiform Encephalopathy Advisory Committee; Dr Robert Will, Head of the CJD Surveillance Unit and a world authority on this disease; Dr Richard Kimberlin, a world authority on scrapie and similar diseases.

The Spongiform Encephalopathy Advisory Committee has itself found no evidence to suggest that there is an emerging CJD epidemic. The Chief Medical Officer, Dr Kenneth Calman, is satisfied that ‘there is no scientific evidence of a link between meat eating and CJD and that beef and other meats are safe to eat’. The international scientists in the World Health Organisation and the European Union have also examined the evidence and believe that beef and beef products are safe to eat.329

5.121 On 18 January 1996, Dr Rubery had responded to Mr Curry stating that ‘as regards the safety of beef your paper is in line with current Government advice’.330 She also pointed out that the quote from the CMO should have read ‘I continue to be satisfied that there is currently no scientific evidence of a link between meat eating and the development of CJD and that beef and other meats are safe to eat’. Mr Skinner had summarised Dr Rubery’s response in the letters he sent on 12 February.331

5.122 On 23 February 1996, Dr Will replied to Mr Skinner. He said:

My view is that there is a remote theoretical risk that BSE in cattle might cause disease in humans. The risk from beef and beef products is likely to be negligible provided statutory measures are fully enforced. I would also agree with the statement that there is currently no scientific evidence that BSE can be transmitted to humans or that eating beef causes CJD.332

5.123 When giving oral evidence to the Inquiry, Professor Will was asked whether the words ‘a remote theoretical risk’ were the right words to have used when at the beginning of February the data available had led him to think it was possible there had been a change in the disease phenotype. Professor Will explained:

I think this is with hindsight. I think you are saying we now know that these cases were significant. At the time we could not be sure about that at all. And you know, I have tried to go through in this statement the various issues that we had to consider that were confounding factors. Of course these applied throughout this time, the issue of ascertainment bias, etc. So my own feeling is that at that time I had not reached a stage at which there was sufficient evidence to make a scientific judgement that there had been a change.333

Further developments in knowledge from late February 1996

5.124 On 26 February 1996, the CJDSU obtained the full regional neuropathology results on three cases of CJD (L, M and J), and in addition, during that same week, a further case was confirmed by neuropathology (case I, identified in January as ‘possible’), bringing the total number of post-1994 confirmed cases of spongiform

329 YB96/1.3/4.2
330 YB96/01.18/9.1
331 YB96/2.12/7.1
332 YB95/2.23/6.1
333 T138 (Will and Eddy), p. 110
encephalopathy in people under 50 years old to ten (D, E, G, H, I, J, K, L, M and P).\textsuperscript{334} In evidence to the Inquiry, Dr Will commented about the significance of these detailed results:

The suspicion of a novel neuropathological phenotype was strongly supported and review of the available pathology in previous cases indicated that all the cases shared a common pathology. Neuropathological re-examination of historical young cases was completed by late February with the exception of the 16-year-old case from 1980. None showed the pathology of the recent young cases.\textsuperscript{336}

5.125 After reviewing the clinical data on the confirmed cases, Dr Will and other colleagues at the CJDSU were further persuaded that the cases in young people shared an unusual clinical phenotype. On 1 March 1996, Dr Will became more confident about this assessment in young people after he had reviewed a patient with suspect CJD whom he had previously seen in early February. In evidence to the Inquiry he said:

The clinical evolution in this case was entirely consistent with the clinical phenotype that we had identified. This was of a major importance in the development of my views about the validity of the proposed clinical phenotype in the young cases. I had not previously seen a similar case of CJD and in general terms it is very much easier to be confident about a clinical phenotype from direct experience.\textsuperscript{337}

5.126 Dr Will explained in his statement his assessment as of 1 March 1996 of the extent to which some of the scientific criteria were met (in relation to judging the significance of the cases). We set this out with an indication of how the position had changed compared with the position at 1 February:

i.

a. is there a novel clinical phenotype?: probable (compared with ‘possible’ on 1 February);
b. is there a novel pathological phenotype?: probable (compared with ‘possible’ on 1 February);
c. are these cases linked to PRNP mutation?: no mutation identified in three cases;
d. is there ascertainment bias or increased efficiency of surveillance?: probable;

ii.

a. are these cases in the UK distinct from previous experience?: probable (compared with ‘possible on 1 February);
b. are these cases only occurring in the UK?: unknown.\textsuperscript{338}

\textsuperscript{334} Dr Will told the Inquiry that Case P was not regarded as a young suspect case of familial prion disease on the basis of neuropathology.
\textsuperscript{335} As noted earlier, these were not the only referred cases under 50 years of age.
\textsuperscript{336} S61 D Will para. 50
\textsuperscript{337} S61 D Will para. 51
\textsuperscript{338} S61 D Will para. 52
5.127 Shortly after the evidence for a novel neuropathological phenotype was established, further genetic information on the cases came to light. Hitherto it had been established that three (D, E and J) of the confirmed cases did not have a genetic basis because mutations of the prion protein gene associated with familial forms of CJD had not been identified. On 4 March 1996, Dr Will received preliminary results from the prion protein gene analysis in four additional cases in people under 50 years. Prion protein gene mutations associated with familial forms of CJD were not identified in three (H, K and M) of these four cases. The fourth case (G) was found to have an insertional mutation of the prion protein gene. These results and the earlier genetic analysis of three of the cases, indicated that six of the confirmed cases of CJD in people under 50 did not have a genetic basis – they were not associated with the familial forms of CJD.

5.128 In early March, Dr Will received the results of the inquiries he had made during February of colleagues in other countries, asking for information on specific cases of CJD aged less than 30 years identified from the world literature. Some of the cases in this age group in other countries had a relatively prolonged illness duration and some an unusual clinical onset, but in only one case were plaques described in the neuropathology. Dr Will’s inquiries into four of these cases confirmed that:

Plaques had not been identified on neuropathological examination in three cases of CJD aged 14, 16 and 20 years from the USA and Canada.

. . . the single case of sporadic CJD that we had identified in the world literature aged less than 30 years with plaque deposition was probably a hereditary form of human prion disease.

5.129 As a result of these developments in relation to genetics and the cases of CJD in patients in other countries, Dr Will explained in his statement that by 8 March 1996, his assessment of the extent to which some of the scientific criteria were met (in relation to judging the significance of the cases) had changed compared with the position at 1 March:

i.  
   a. is there a novel clinical phenotype?: probable;  
   b. is there a novel pathological phenotype?: probable;  
   c. are these cases linked to PRNP mutations?: no mutation identified in six cases (compared with three cases on 1 March);  
   d. is there ascertainment bias or increased efficiency of surveillance?: probable;  

ii.  
   a. are these cases in the UK distinct from previous experience?: probable;
b. are these cases only occurring in the UK?: possible (compared with ‘unknown’ on 1 March).\(^{341}\)

\textbf{5.130} Dr Will explained further in his statement:

By early March we had concluded that there was sufficient evidence to be confident that we had identified and characterised a novel clinicopathological phenotype of CJD . . . It is important to stress that although we believed we had identified a new form of CJD, novel clinicopathological variants of CJD had been identified in the past both in the UK and in other countries. In order to indicate a link between BSE and ‘new variant CJD’ it was essential to determine whether similar cases were occurring in other countries.\(^{342}\)

\textbf{5.131} Dr Will and Dr Ironside presented a paper summarising their findings at the 25th SEAC meeting on 8 March 1996.\(^{343}\) The paper entitled ‘Human TSE Epidemiology – The Emerging Picture’ described the identification of a subset of CJD with an early age of onset, long duration of illness, no prion protein gene mutations, ‘florid’ plaques throughout the brain and extensive prion protein deposition.\(^{344}\)

\textbf{5.132} Dr Will reported further on the two subsets of sporadic CJD. The CJDSU had found that:

There appeared to be two distinct subsets of sporadic CJD cases. The first with extended duration of illness with plaques in the brain and spinal cord, and the second with a short duration of illness which did not show these features. The presence of plaques in the spinal cord might be related to the extended duration of illness which allowed time for centrifugal spread of PrP down the spinal cord . . . The pathology in the sporadic cases in young people was different to the two subsets mentioned above.\(^{345}\)

\textbf{5.133} Dr Will also reported that the UK cases had been compared with the 17 cases in patients under 30 years of age that had been found world wide since 1965.\(^{346}\) The clinical features and the duration of the illness were variable in these 17 cases, there was no genetic information available, and in all but one case (thought to be hereditary) there were no plaques recorded. They had concluded that the cases in young people in the UK with their unique pathology and similar clinical features ‘could be’ a new form of CJD.

\textbf{5.134} By this time, 8 confirmed cases of the new phenotype had been identified (D, E, H, I, J, K, L, and M).\(^{347}\) All were aged under 50. In addition, one case had undergone a biopsy that was negative but had clinical symptoms of CJD (O) and post-mortem and neuropathology results were awaited for two further patients, cases R and S. The minutes from the SEAC meeting record that:

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\(^{341}\) S61D Will para. 52  
\(^{342}\) S61D Will para. 56  
\(^{343}\) YB96/3.8/1.1–1.11  
\(^{344}\) YB96/3.8/1.5–1.6; SEAC25 tab 3  
\(^{345}\) YB96/3.8/1.6 para. 22  
\(^{346}\) YB96/3.8/1.6 para. 23  
\(^{347}\) This excludes G, which was established to be a case of prion gene mutation, and P, which was thought to be and later confirmed as a case of prion gene mutation
Dr Will and Dr Ironside were of the opinion that the young cases in the UK with their unique pathology and similar clinical features could be a new form of CJD. They intended to publish the findings in a peer-reviewed journal such as *The Lancet* as soon as possible. They preferred for the findings to be kept confidential until then, but would be prepared for them to be made public now should the Committee and Government consider that necessary.\(^{348}\)

5.135 Much discussion followed this presentation. Members of SEAC queried whether these cases had only been identified because of improved case identification and whether this new form of CJD could have been present, but unidentified, in the population for some time. Dr Will and Dr Ironside did not believe that this was the case as awareness of CJD had been growing in neurologists over a number of years, identification had been based on neuropathology, and the pathology was very different to that in young cases outside the UK. Referral bias, due to increased awareness of CJD, was considered.\(^{349}\) However, the increase in CJD awareness should have also caused referral bias in other countries and as similar young cases had not been seen in other countries, referral bias as an explanation of the increase of young CJD cases was ruled out.

5.136 The minutes record that Professor Pattison (Chairman) closed the discussion by confirming that:

... the Committee would keep the information confidential pending publication of the paper by Dr Will and Dr Ironside. He would inform the Chief Medical Officer and the Chief Veterinary Officer of the findings and SEAC’s concerns. It would be for Ministers to decide whether or not they should be put into the public domain now.\(^{350}\)

5.137 On 13 March 1996, the diagnosis of new variant CJD was confirmed by brain biopsy in the case Dr Will had seen on 1 March 1996, a 31-year-old (case S). This brought the total number of confirmed (non-familial) CJD cases in young people to nine.\(^{351}\) In his statement to the Inquiry, Dr Will said that ‘review of the results of inquiry on risk factors for CJD had not shown any common or recognised risk factor for the development of CJD in these young cases’.\(^{352}\)

5.138 On the same day, the neuropathological findings in the 16-year-old case who died in 1980 became available. These findings showed an appearance consistent with sporadic CJD. No plaques were identified, even with biochemical staining for prion protein.\(^{353}\)

5.139 Dr Will told us that during March evidence became available to indicate that the novel phenotype of CJD was restricted to the UK, suggesting a link with BSE:

In March 1996 I contacted my colleagues in the European surveillance system and requested further details on the young cases that had been identified in participating countries. I requested details of the clinical

\(^{348}\) YB96/3.8/1.6
\(^{349}\) S61 Will para. 42
\(^{350}\) YB96/3.8/1.8
\(^{351}\) S61D Will para. 57. This figure of nine refers to cases later classified as vCJD. There were other young cases of CJD which were either sporadic or familial cases
\(^{352}\) S61 Will para. 43
\(^{353}\) S61D Will para. 57
characteristics during disease evolution, the results of EEG examination and details of the neuropathological appearances, if available. My colleagues kindly responded promptly and it became apparent that none of the young cases in continental Europe had the clinical and pathological phenotype of the young cases in the UK. This evidence indicated that the novel phenotype of CJD was restricted to the UK, consistent with a causal link with BSE.\(^{354}\)

5.140 An emergency meeting of SEAC was held on 16 March 1996 to discuss the new variant CJD cases in detail.\(^{355}\) Dr Will reiterated the description of the new variant of CJD and the CJDSU had identified: early age of onset, initial presentation with psychiatric or behavioural problems, long incubation period,\(^{356}\) abnormal EEG, distinct histopathology with large plaques. He also presented full details of all the ‘variant’ CJD cases including the newly identified ninth case.\(^{357}\)

5.141 Dr Will reported on the CJDSU analysis of archival CJD cases. All cases under the age of 40 had been examined in detail and no evidence of the unusual characteristics of the variant form of CJD had been detected. He also referred to the literature search of young cases of CJD from around the world. Again none of the unusual characteristics of this variant form of CJD had been detected. Therefore, Dr Will concluded that ‘the new variant form of CJD was a distinct form which was partly age related, notably having an excess of cases in people under 30’.\(^{358}\)

5.142 The minutes of this SEAC meeting also record that the CJDSU pathological material had been reviewed by three other pathologists, all with experience of spongiform encephalopathies and their independent view was that ‘this was a distinct entity unlike any previously seen form of CJD’.\(^{359}\)

5.143 The genetic analysis of six of the nine cases was discussed.\(^{360}\) Complete DNA sequencing of the prion protein gene had been performed in the six cases and no mutations had been detected, thereby ruling out familial CJD. Geographical spread and the medical histories of the cases were discussed but no common factor between the cases could be identified.

5.144 In conclusion, the Committee agreed that this new variant of CJD was a distinct entity, although it was uncertain whether it was a new form of the disease or represented clustering linked to a new risk factor.\(^{361}\) It was agreed that ‘they must take very seriously the possibility that this new risk factor was BSE, although it was noted that the data did not allow this conclusion to be drawn firmly’.

5.145 On 19 March 1996, the 28th meeting of SEAC was convened in response to a request from the Government for advice on the significance of the findings about a new form of CJD and to provide recommendations for any action.\(^{362}\) The minutes record that the intention was for SEAC to provide this advice by early the following day for discussion by the Cabinet in preparation for Ministerial statements.\(^{363}\)
Further details of the deliberations at the meeting on the adequacy of control measures at that time to protect animal and public health, and SEAC’s advice to the Government are given in vol.6: *Human Health, 1989–96* and in vol.11: *Scientists after Southwood*.

5.146 Dr Will reported to the meeting that a tenth case of the new form of CJD had been confirmed post-mortem in a 20-year-old (case R). He added that the genetic analysis of seven out of the ten cases would be completed on the following day. Whilst there was so far no evidence of a genetic mutation, Professor Collinge commented ‘that there was only a small possibility that the genetic sequencing would provide any information to change the view SEAC had reached at its meeting on the 16 March’.364

5.147 The following day SEAC resumed the meeting to continue their discussions of the options for additional measures and to decide on the Committee’s advice about the risk to human health from eating beef.365 Their discussions and recommendations are described in vol. 6: *Human Health, 1989–96*.

5.148 As a result of these developments, Dr Will confirmed in his statement that by 20 March 1996, his assessment of the extent to which some of the scientific criteria were met (in relation to judging the significance of the cases) had changed compared with the position at 8 March:

i.

a. is there a novel clinical phenotype?: probable;
b. is there a novel pathological phenotype?: probable;
c. are these cases linked to PRNP mutations?: no mutation identified in six cases (compared with three cases on 1 March);
d. is there ascertainment bias or increased efficiency of surveillance?: probable;

ii.

a. are these cases in the UK distinct from previous experience?: probable;
b. are these cases only occurring in the UK?: probable (compared with ‘possible’ on 8 March).366

**Relevant events after 20 March 1996**

5.149 Several differences between classical CJD and variant CJD have been identified in the course of subsequent surveillance which supported the conclusion that vCJD was a new entity. These differences are in the age of onset, the clinical symptoms, the characteristics of electroencephalogram and in the disease pathology.

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364 YB96/3.19/1.2
365 YB96/3.20/1.1–1.7
366 S61D Will para. 60
i. **Age.** The median age in classical CJD at death was 66 compared with 29 for vCJD. The median illness duration from the first symptom to death was 4 months in classical CJD but 14 months for vCJD. 367

ii. **Clinical symptoms.** With vCJD, the clinical presentation was found to be with both behavioural and psychiatric disturbances. After several weeks or months, a progressive cerebellar syndrome developed with poor gait and poor limb muscle coordination. Dementia usually occurred later in the clinical course.

iii. **Electroencephalogram (EEG).** In vCJD patients with EEG showed no abnormality, in contrast to most classic CJD patients where unusual wave patterns can be observed. 368

iv. **Pathology.** Significant differences in the neuropathology of vCJD patients were observed compared to classic CJD patients. These included ‘florid plaques’ in the cerebral and cerebellar cortex; abundant prion protein deposition in all brain areas with irregularly shaped deposits around neurones and blood vessels in the cerebrum and cerebellum; spongiform change most marked in basal ganglia; and severe thalamic gliosis (proliferation of the glial or supporting cell in the brain). 369 Another unique feature in vCJD patients was found to be the presence of prion protein outside the central nervous system. Unlike other forms of CJD, the prion protein accumulated in the lymphoid tissue of vCJD patients. 370

5.150 The CJDSU considered in depth the possibility of a causal link between BSE and vCJD, the main factors being:

i. The timing of the occurrence of vCJD in relation to the emergence of the BSE epidemic, and what is known about the incubation periods of other human TSEs.

ii. The occurrence of two new diseases, BSE and vCJD, almost exclusively in the UK.

iii. Similar biochemical characteristics.

Investigation of these factors revealed compelling evidence that vCJD is caused by BSE. (The evidence linking the two diseases is described in detail in vol. 2: *Science.*)

5.151 The epidemiological data gathered by the CJDSU did not however identify a specific risk factor, including a specific dietary risk factor, linking the patients as distinct from controls. 371 Such a failure to find a common dietary factor was considered to be a result of constraints in the methodology of the study rather than the absence of a link. Food questionnaires are very difficult to administer, especially for vCJD where information dating back many years was sought from the relatives of patients who might have been subject to recall bias. Even if the information was available, interpretation of the information was made difficult because it is not

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367 T24 p. 5
368 T24 p. 88
369 S60 Ironside Annex 2; T24 p. 9
371 T24 pp. 24–5
known which human food products are likely to be contaminated by BSE and to what level. The critical issue, in Dr Will’s opinion, was whether the food products contained brain and spinal cord tissue. He considered that the major risk was most likely from products containing mechanically recovered meat. (The administration of the questionnaire is an area in which it has been suggested that the PHLS could have played a role in the surveillance of CJD, given the considerable experience of the organisation in the investigation of emerging diseases. The question of PHLS involvement in CJD surveillance is discussed in Chapter 3 and paragraphs 5.171–5.173.)

**Update on cases of CJD in farmers**

5.152 During the period 1986–96, much attention and publicity was focussed on four cases of CJD in farmers (see above). Although those four cases were regarded as likely to be more than might be expected for the known population frequency of the disease, analysis of CJD in Europe showed the incidence of disease in farmers was similar to that in the UK. In addition, the clinical and pathological features of these cases were no different to those found in classical sporadic CJD.

5.153 It is understood that since 20 March 1996, at least two further cases of sporadic CJD in a relevant occupational group have been reported to the CJDSU, one in a farmer and another in an abattoir worker. Recent transmission studies in mice indicate that the causal agent in these cases has transmission characteristics (incubation period and neuropathology) which are distinct from both vCJD and BSE, and that the protein deposited in the brain in all of these cases has a glycosylation pattern distinct from the type 4 pattern observed in vCJD and BSE.

**Update on suspect cases of CJD in teenagers**

5.154 The four cases A, D, E and R mentioned previously have all been confirmed post-mortem as having died of CJD. Case A had a long duration of illness and the EEG did not show the classical CJD pattern, but the neuropathology was not typical of vCJD, the lymphoreticular system was not affected and there was a type 2 glycosylation pattern as found in sporadic CJD; there was no prion mutation and the genotype at codon 129 was heterozygous methionine/valine (MV). Strain typing was undertaken but the result is not yet available. In cases D, E and R the neuropathology showed florid plaques and the glycosylation pattern was reported as type 4, the type similar to BSE. Lymphoreticular tissue contained deposits of \( \text{PrP}^{\text{Sc}} \). Prion gene mutations were not found, and the genotype at codon 129 was homozygous for methionine (MM) as in all subsequent vCJD cases with the characteristic clinical and neuropathological features described for this condition.

5.155 In his evidence to the Inquiry, Professor Will agreed that vCJD might present differently in patients with different genotypes at codon 129. Patients with the genotype MM might be expected at an earlier stage of the epidemic than patients with other genotypes. At the same session, Dr Ironside noted that when BSE was transmitted to mice carrying the human \( \text{PrP} \) gene with valine at codon 129, the glycoform pattern was slightly different from the pattern found in methionine...
homozygotes. This new, type 5 pattern might be expected should BSE cause disease in humans with a VV or MV genotype.\textsuperscript{376} So far, no case of CJD has been identified with a type 5 pattern and, in particular as noted above, case A was shown to have a type 2 pattern.

**Future incidence of vCJD**

5.156 By 4 September 2000, the total number of definite and probable cases of vCJD was 82. Table 5.1, below, gives the numbers of these cases identified each year since 1995.

<table>
<thead>
<tr>
<th>Year</th>
<th>vCJD cases in the UK</th>
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<tbody>
<tr>
<td>1995</td>
<td>3</td>
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<tr>
<td>1996</td>
<td>10</td>
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<td>1999</td>
<td>14</td>
</tr>
<tr>
<td>2000 (to 4 September)</td>
<td>27\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Includes probable cases still alive and probable vCJD deaths awaiting post-mortem results.

Source: CJD Surveillance Unit

5.157 The many variables associated with the disease (such as route of exposure, dose, incubation period, genetic susceptibility, etc) make predicting the possible number of future cases difficult. This is evidenced by the large variations in predicted numbers of cases calculated using different statistical models. Predictions on the future incidence of vCJD are discussed in detail in vol.2: *Science*.

**Discussion on the work of the CJD Surveillance Unit (CJDSU)**

5.158 While the Southwood Working Party judged that the risk of transmission of BSE to humans appeared remote, they made the reasonable assumption that, if BSE did transmit, the clinical disorder would closely resemble Creutzfeldt-Jakob disease. They recommended the monitoring of cases of CJD through the neurological network with particular emphasis on occupational groups exposed to bovine tissues, and suggested that the new Consultative Committee on Research chaired by Dr Tyrrell should consider arrangements for surveillance.

5.159 Dr Will presented a paper to the Tyrrell Committee in April 1989 on the surveillance of the population for CJD based on the studies he had done as a research registrar with Professor Bryan Matthews in 1979–82. The *Tyrrell Committee Report* recommended CJD surveillance and a grant application based on Dr Will’s report was accepted by the Department of Health, and the CJD Surveillance Unit (CJDSU) started work in May 1990.
The worst fears of officials and advisors were realised when, on 8 March 1996, the CJDSU reported to SEAC that they were of the opinion that cases in ten young people could be a new form of CJD. The circumstantial evidence of a link with BSE led to the public announcement on 20 March 1996.

**Could vCJD have been identified earlier?**

There were indications from 1993 onwards that the CJDSU might indeed detect atypical cases or changing patterns in the incidence of CJD. We have summarised in this chapter the referrals to the CJDSU of cases of CJD in young people, beginning with case A which came to the attention of Dr Will in 1993, and cases of CJD in farmers whose farms had a history of BSE. With hindsight, we know that the farmers and some cases in young people have not been established as vCJD. However, the majority of cases of CJD in young people referred to the CJDSU by the end of 1995 have now been established to be vCJD. Only one of the CJD patients from the UK had been diagnosed in their teens (in 1980) prior to the emergence of BSE. The concern of Dr Will and Professor Collinge that so many young patients had been identified in such a short period was noted in the minutes of the SEAC meeting of 5 January 1996. In late 1995, Dr Will had noted that three of the cases were unusual in that pathological examination had revealed extensive plaque deposition in the brain. Why was it not until March 1996 that the CJDSU concluded that there was indeed probably a new variant of CJD?

Dr Will considered factors which might have led to increased identification of young patients since 1994:

i. **Ascertainment bias.** Young patients might have been wrongly classified as subacute sclerosis panencephalitis in the past. However, a review of patients with this diagnosis revealed no cases of CJD.

ii. **An increased post-mortem rate.** This could have led to an increased chance in identifying atypical cases in young patients.

iii. **The availability of immuno-chemistry for PrPSc.** This technique was increasingly available in the 1990s and had great diagnostic value.

At the 23rd meeting of SEAC on 5 January 1996, Dr Will listed four definite cases and one possible case under 30 years of age, along with two confirmed cases and one suspect case aged between 30 and 40. Several days later, the possible case under 30 had been confirmed by neuropathology as had a case in a patient aged 41. In his assessment of the significance of the cases, Dr Will sought up-to-date information from the European surveillance project on CJD. This revealed that between 1993–96 there were five recorded deaths within the age range 20–39. Excluding the teenagers, this age distribution was similar to the UK distribution of cases.

Dr Will then reviewed the clinical presentation and course of illness in the young cases and this revealed:

i. a relatively prolonged duration of illness;

ii. early psychiatric symptoms;
iii. absence of the EEG pattern characteristic of sporadic CJD; and
iv. prominent ataxia.

5.165 By the end of January, the clinical phenotype and the unusual neuropathology had been recognised by the CJDSU. Similar features had been associated occasionally in both sporadic and familial CJD. Three of the cases had been tested and shown not to have prion gene mutations. They were noted also to be homozygous for methionine at codon 129. Arrangements were made to check for prion gene mutations in the remaining patients. (These results for a total of six patients were available on 4 March 1996.)

5.166 By early March, Dr Will had obtained from European colleagues information on the clinical presentation, phenotype and neuropathology on young patients with CJD identified in continental Europe. The clinical features and duration of illness were variable in these cases and did not follow the pattern that had been recognised in the young cases in the UK. This was confirmed by a literature search of other young cases of CJD from around the world. It appeared probable that the CJD of young patients recognised in the UK was a new variant, unrecognised elsewhere.

5.167 By 13 March 1996, the number of UK patients under the age of 50 with the new phenotype of CJD was nine.377 This number excluded one case found to have a prion gene mutation. All were homozygous for methionine at codon 129. All had the characteristic phenotype with psychiatric presentation and a relatively long duration of illness. It had been confirmed by three external referees that the pathological features, including prominent plaques, constituted a novel type of CJD, previously unreported.

5.168 It is clear that since the summer of 1995, the key question in the forefront of the minds of Dr Will and his colleagues concerning the young patients with CJD was whether or not there could be a link with BSE. On 8 March 1996, Dr Will and Dr Ironside presented their reasons for concluding that cases in young people could be a new form of CJD. Review of the medical histories of the young patients revealed no common risk factor which might explain the occurrence of their condition. At their meeting on 16 March, SEAC agreed that ‘They must take very seriously the possibility that this new risk factor was BSE, although it was noted that the data did not allow this conclusion to be drawn firmly’.

5.169 We believe that the presentation to SEAC on 8 March 1996 could not have been made sooner. It was necessary to establish the clinical and pathological characteristics of the condition in a sufficient number of patients to justify the conclusion that a new variant of CJD had been identified. The findings had to be checked by independent scientists and clinicians, and it had to be shown that what appeared to be a new variant was not in fact a type of CJD previously reported in young people, either in the UK or abroad, before the BSE epidemic. Furthermore, the DNA of each patient had to be analysed to exclude a disease-producing mutation of the prion gene. These were all prerequisites to the conclusion that there was a new variant of CJD which was probably linked with BSE. The time taken to establish a link with BSE does not warrant criticism. A wrong conclusion, hastily drawn, could have created unwarranted public anxiety and could have been very damaging to public confidence.

377 This number excludes G and P, for reasons noted earlier.
Could PHLS have been usefully involved in surveillance?

5.170 We now turn to consideration of the procedures in place for CJD surveillance. It is hard to see what alternatives to the CJDSU could have been more effective. The CJDSU was a research unit, established on the basis of a remote possibility that BSE might be transmitted to humans. It was sensible to have a dedicated unit to monitor a comparatively rare and complex group of disorders for which there was no laboratory test. The decision to place the responsibility for surveillance with a small research team of dedicated medical scientists headed by a clinical neurologist with extensive experience in CJD was entirely correct. The CJDSU was a research unit whose work deserves nothing but praise.

5.171 It is unlikely that existing institutions responsible for monitoring public health would have achieved the same result in as short a time. The OPCS (later the Office of National Statistics) is experienced in monitoring health trends but is largely dependent on death certification. While this may be sufficient for indentifying trends in relatively common causes of death, the procedure is inefficient for rare complex disorders in which diagnosis is difficult. The correct certification of causes of death is notoriously unreliable and especially so for a condition like CJD which can be mistaken for other more common neurodegenerative disorders such as Alzheimer’s disease. In such circumstances, the underlying diagnosis may even be omitted and the immediate cause of death recorded, for example bronchopneumonia.

5.172 There has been much discussion about whether or not the PHLS could have provided surveillance of CJD. The PHLS was established in 1940 to monitor infectious disease in the community and to provide laboratory diagnosis for many zoonotic disorders. They have a network of laboratories throughout England and Wales and many other resources including epidemiologists, statisticians and field workers. They have access to medical registers in the NHS and close links with clinicians. However, in 1989 they did not have expertise in CJD and most importantly there was (and still is) no established laboratory test for either CJD screening or for diagnosis in suspect cases. None the less, we believe that, short of undertaking CJD surveillance themselves, the PHLS could have given considerable assistance to the CJDSU. They might have provided expertise in epidemiology based on their experience of work in the field of investigating disease outbreaks. Their field epidemiologists could have been involved in designing questionnaires, interviewing relatives and in collecting unbiased answers designed to explore aetiological factors. They had the resources to conduct active surveillance throughout the UK through polling neurologists and other relevant groups of clinicians and compiling null returns in addition to suspect cases. They could have provided access to medical registers, hospital in-patient and out-patient statistics and an efficient system of communication within the PHLS network. They could have helped to look for potential routes of infection between cattle and humans, for example by investigating possible associations with vaccines prepared from bovine products. In these and other respects, the PHLS could have contributed to the CJDSU surveillance of CJD and their programme of epidemiological research. These comments in no way detract from the sterling work of the CJDSU team who so promptly detected the emergence of vCJD and so efficiently established the clinical and pathological characteristics of the disease. While assistance from the PHLS could have been valuable, it would not have enabled identification of vCJD at any
earlier date. We do not criticise those who concluded that the task of monitoring CJD should be left to the Surveillance Unit.

Was there adequate communication of information to the Department of Health?

5.173 We now turn to consider whether the communication of information from the CJD Surveillance Unit to the Department of Health was adequate. The only matter that gave us concern in this regard was Dr Will’s reply to Mr Skinner on 23 February 1996. In his reply to Mr Skinner on 23 February 1996, Dr Will stated that ‘There is a remote theoretical risk that BSE in cattle might cause disease in humans’ and ‘that this is likely to be negligible provided statutory measures are fully enforced’. He added that he agreed with the statement that ‘there is currently no scientific evidence that BSE can be transmitted to humans and that eating beef causes CJD’. Dr Will stressed to us that at this time there were ‘a whole range of issues that had to come together’ before he reached a stage at which he considered there was sufficient evidence to make a scientific judgement that there had been a change. This range of issues included genotyping results, reaching more conclusions about the neuropathology and the clinical phenotype and other issues. The word ‘currently’ in Dr Will’s reply to Mr Skinner did not preclude the materialisation of any new evidence. In the event, that new evidence was announced only four weeks later.

5.174 We have given our reasons above (paragraph 5.170) for concluding that the CJD Surveillance Unit could not have informed SEAC of the emergence of a new version of CJD earlier than 8 March 1996. It was not until about 13 March that Dr Will was sure that the novel clinical phenotype had not been reported outside the UK, that the distinct neuropathological findings had been confirmed by independent pathologists, and that prion protein gene mutations were not involved. Until this information had been assembled Dr Will did not feel in a position to make a scientific judgement that there was evidence that BSE could be transmitted to humans.

5.175 However, we note that some inkling of what was to come is to be found in the minute dated 1 March from Mr Eddy to Mr Haddon, Mr Meldrum, Mr Taylor and Dr Render, in which it is indicated that the Department of Health had been informed that the results were beginning to look rather firmer and that there was a new sub-population of the disease emerging. We do not think that Dr Will was able to go this far on 23 February and we consider that his presentation to SEAC on 1 February had given Mr Skinner a fair picture of the degree to which his thinking had progressed. In these circumstances, we do not think that Dr Will can be blamed for continuing to be cautious in his reply to Mr Skinner on 23 February 1996.378

378 We consider in Chapter 7 of vol. 6: Human Health, 1989–96 our concerns in relation to the adequacy of communication within the Department of Health and MAFF during the period leading up to 20 March 1996.
Was involvement of the CJDSU in the public debate about the safety of beef appropriate?

5.176 The difficulties that arose from involvement of the CJDSU in the public debate are illustrated by the Parliamentary Food and Health Forum on 20 February 1996 at which Dr Will was an invited speaker. At that meeting Dr Will found himself obliged to deal with the question whether the age distribution of CJD appeared to have changed in the past year. During his talk, he stated that current evidence did not suggest any definite change in the pattern of CJD that could be attributable to BSE and that there was no overall change in the age-specific incidence of CJD in the UK. He was recorded in a note of the meeting as stating that current information was reassuring and that any risk to man from BSE might not be evident for some years. Four weeks later, results of key investigations had been completed and different conclusions had been drawn.

5.177 Dr Will stated to us that his view at this time was that there was no overall change in the age specific incidence of CJD in the UK. He stated that this view was based on the statistical analysis provided by Dr Gore on 5 February 1996. Dr Gore’s calculations were based on the first of four young cases of confirmed CJD (aged 16, 19, 29 and 30 years) which had occurred during the 5-year-period between 1990–96. When considered in relation to the three young cases (aged 35, 36 and 38 years) occurring in the previous quinquennium, the probability of observing four cases was not expected. No account was taken of the younger ages of the four cases, nor of the fact that by 20 February 1996, eight cases under the age of 40 were known. Statisticians approach these matters by attempting to assess the likelihood that the cases in question may represent no more than random events. If the probability of the cases in question being a random event is less than 5 per cent then they would normally be thought to have statistical significance. The probability of eight cases occurring by chance was now 0.03, ie within the 5 per cent probability to which statistical significance is generally ascribed. It was therefore not strictly correct to conclude that there had been no statistically significant change in the age distribution of cases in the UK.

5.178 Although the numbers had just achieved formal significance levels, we believe that Dr Will had reason to be cautious about the implications of his findings. Before coming to a conclusion that there might be a link with BSE, it was necessary to make sure that the eight cases had a consistent phenotype. Dr Will was correct in waiting for the results of genetic analysis on 4 March 1996 and for the independent expert review of the pathological material. He had to be sure that similar cases had not occurred outside the UK during the same period. It was this that provided the circumstantial evidence of a link with the BSE epidemic. All the pieces of the jigsaw puzzle were not in place until mid-March 1996 and Dr Will did not feel confident to suggest the existence of a link with BSE until they were.

5.179 Dr Will has explained his reticence at the Food and Health Forum meeting about his concerns about CJD in young patients. He believed that it would be premature to make a public announcement before he was satisfied that all aspects had been fully examined and the results peer-reviewed. An announcement of a change in numbers of young patients over such a short period might have precipitated a crisis of some magnitude based on the unsupported assumption that
the changes were due to BSE. It was imperative that other explanations had to be rigorously investigated before coming to such a conclusion.

5.180 Undoubtedly the recognition of an increasing number of young people affected with CJD in late 1995 and early 1996 placed the CJDSU in a difficult position if asked publicly about a possible link with BSE before investigations on the patients had been completed. The position was particularly acute for Dr Will on 20 February. Although he was concerned about the cases of CJD in young people, he felt he could not publicly refer to the change in the number of young patients.

5.181 We have some sympathy for Dr Will in the situation in which he was placed. The CJDSU are to be commended on the sound work that they had done in identifying the new variant of CJD. It is unfortunate that Dr Will found himself in a position where he was required to speak in public about the risk that BSE might cause disease in humans. With hindsight, it might have been better for him to have refrained from making any comment, and from participating in the Food and Health Forum, until his investigations were complete. Given the position in which he found himself, we do not criticise Dr (now Professor) Will.

Is a link between BSE and vCJD established?

5.182 As set out in more detail in vol.2: *Science* (Chapter 4), the link between BSE and vCJD, suggested on the circumstantial evidence that the two conditions were associated in both time and space almost exclusively in the UK, was soon supported by experimental and biochemical results. Chief among these were the strain typing results in mice which revealed in 1997 that BSE and vCJD had similar incubation periods and lesion profiles in the brain. Type 4 glycosylation patterns were found in both, and studies using transgenic mice in which the murine prion gene had been replaced by the bovine gene strongly suggested that the infective agent was identical in both conditions. Present evidence seems overwhelming.

Some observations about vCJD that call for explanation

Why does vCJD seem to be a disease of young people?

5.183 In sporadic CJD the median age at death for the period 1995–99 was 65 years. The median age at death in vCJD, based on the experience to 31 December 1999, is 29 years. The median age at onset in vCJD is 28, with the youngest case aged 14 years while the oldest case was aged 53 years. We have identified two main theories about the age of current cases that have led to much speculation. These are diet and the use of vaccines.

5.184 In the case of diet it has been suggested that various types of processed meat including beefburgers, sausages and meat pies may have contained beef brain and spinal cord as ingredients. No tissues from BSE-affected animals should have entered human food after the introduction of the slaughter and compensation policy in August 1988. Brain and spinal cord from cattle incubating BSE ought not to have entered human food after the SBO ban in 1989. However, spinal cord may have

379 Eighth Annual Report of the CJDSU, p. 8
380 Eighth Annual Report of the CJDSU, p. 13
381 Eighth Annual Report of the CJDSU, p. 13
done so, along with dorsal root ganglia, as contaminants of mechanically recovered meat (MRM) obtained from bovine vertebral columns up to December 1995. MRM might also have been included in baby foods, although to what extent is uncertain. We refer in vol. 2: *Science* (Chapter 4) to a study in which the consumption of processed beef products was examined in relation to age in a group of individuals aged 15 years and over. In the case of beefburgers, the age distribution fell steeply with age, and was to some extent correlated with age distribution of vCJD patients. The consumption of beef, sausages and meatpies was not age related. The suggestion is that the risk of infection is greater in children and young adolescents because their diet includes more beefburgers than older individuals.

5.185 Vaccines have been identified as a possible source of infection because, although they do not directly contain bovine ingredients, tissue culture media such as foetal calf serum or bovine serum albumin or, less commonly, bovine brain and spleen, may be used during their production. We discuss in vol. 7: *Medicines and Cosmetics* steps taken to close this possible pathway of infection. We also discuss in that volume tests undertaken by the NPU to ascertain whether bovine blood and serum could transmit infectivity to mice. The results of this particular piece of research were negative, which provides some reassurance about the safety of vaccines. Nevertheless, these tests were not conclusive and the possibility that such material may have transmitted infection calls for consideration:

i. During childhood, vaccines are routinely administered at three stages: namely infancy, the 4–5-year-old age-group and the 10–13-year-old age-group. A starting-point in considering whether vaccines are implicated in transmission is to look at whether any known cases of vCJD might be attributable to childhood vaccination at these ages. It has in the past been suggested that this is unlikely, in particular because of the widely held belief that the earliest cases of BSE did not occur until the early 1980s. As the majority of patients with vCJD were born before 1980 (the youngest in 1985), some have assumed that vaccination in childhood would have been completed in most cases well before vaccines could possibly have been contaminated.

ii. However, current epidemiological evidence (see vol. 2: *Science*) is consistent with the possibility that there was a small number of cases of BSE as early as 1970–72, and that these were followed by three successive waves of the disease in 1975–77, 1981–84 and 1986–87, as a result of recycling of BSE in MBM. Batches of vaccines manufactured during the 1970s cannot therefore be ruled out as a source of infection merely because of their date of manufacture. Patients with vCJD born before 1960 are unlikely to have been infected by childhood vaccination, but the possibility of infection via vaccinations in adulthood may merit consideration.

iii. These possibilities should be taken into account in an analysis of the specific batches of vaccines administered to victims of vCJD, and consideration given to whether there is any common batch or other factor.

5.186 An *ad hoc* Working Party of the Committee on Safety of Medicines which considered BSE-related issues associated with the use of seedlots$^{382}$ in vaccines

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$^{382}$ The master stocks from which each batch is derived
noted that all vaccines in current use are prepared using bovine materials sourced from BSE-free countries (mostly Australia and New Zealand). UK-sourced bovine material was used in a number of vaccines prepared from 1980 to 1989 and distributed up to 1992. Other vaccines and seedlots were prepared prior to 1980, but the sources of bovine ingredients in these have not been identified. The Working Party noted that both human and cattle vaccines prepared with UK-sourced bovine materials have been widely distributed throughout Western Europe without apparently being associated with outbreaks of either vCJD or BSE. This is taken as a strong argument against the possibility that vaccines have been vectors of either disease.

5.187 It will be apparent that some of the assumptions made by the Working Party of the CSM are open to question for reasons we have set out in our Report. We hope that government will look at the topic again in the light of our comments.

Is there evidence of clustering of vCJD cases?

5.188 The 1999 Annual Report of CJDSU draws attention to the geographical distribution of cases of vCJD (see Figure 5.1, in which the data have been further updated) and shows that if the UK is divided into ‘North’ and ‘South’ regions, the rate per million individuals aged between 16 and 54, is 2.57 for the ‘North’ region and 1.30 per million individuals for the ‘South’. An early suggestion of a cluster of four cases in Ashford, Kent was considered not to have significance. More recently, a group of four deaths from vCJD in and around the village of Queniborough, Leicestershire, plus another probable case from the same area, has aroused intense media interest. Both the CJDSU and PHLS are making detailed local enquiries. We hope that the opportunity to investigate such clusters will provide information on common factors and lead to a firm conclusion about the source of infection and its route to affected patients. Such knowledge will improve understanding of the disease and hopefully lead to strategies for treatment.
Why have all cases of vCJD tested to date been homozygous for methionine at codon 129 on the prion protein gene?

5.189 This is presumably because this particular genetic polymorphism is a susceptibility factor to BSE infection. We know that 70 per cent of sporadic CJD patients are similarly homozygous for methionine at codon 129. However, 39 per cent of the general population shares this genotype, of which only a tiny number have succumbed to CJD of any type. This suggests that methionine homozygosity
at codon 129 is only one of a number of susceptibility factors. Other yet undiscovered genes outside the prion protein gene locus might also confer susceptibility. If these postulated genes have a major effect on susceptibility this could lead to familial clustering. Alternatively, it might indicate that only a small proportion of the susceptible population was exposed to BSE infection in the 1970s and 1980s, as might be expected with only limited distribution of the agent in food or vaccines.

5.190 It has been observed in iatrogenic CJD due to human growth hormone contamination, that the age of onset is earlier in methionine homozygotes than in valine homozygotes. This raises the possibility that cases of vCJD with other genotypes at codon 129 will emerge in due course in older patients who have been incubating it for longer. We note that the CJDSU is alert to this possibility, and also to the possibility that the clinical phenotype in such cases might differ from present cases of vCJD.

Why have all patients with vCJD so far investigated shown signs of high levels of infectivity in tonsils and other parts of the lymphoreticular system, whereas cases of sporadic and iatrogenic CJD have not?

5.191 It has been postulated that this observation implies infection via the gastrointestinal tract in vCJD, while iatrogenic CJD is due to parental inoculation, and sporadic CJD arises by somatic mutation or by toxic conversion of PrP\(^{C}\). It has also been suggested that infections of the tonsils and gastrointestinal tract due to other pathogens may increase susceptibility to TSE agents by increasing their absorption through inflamed tissues. Studies on the incidence of past disease in subjects and controls might shed light on this possibility.

Is occupation a risk factor in vCJD?

5.192 One of the original proposals in the CJD surveillance project was to monitor occupational groups exposed to BSE-affected cattle and their products. Such groups include farmers, veterinarians, slaughtermen and butchers. This part of the project was given a low priority by the Tyrrell Committee and was not implemented. It was felt that rather than set up longitudinal study of a fixed number of individuals in each group, together with matched controls, it would be adequate to take an occupational history of each CJD case at the time of referral.

5.193 From 1990 to 1996, the CJDSU had referred to it four farmers affected with CJD who were known to have had cases of BSE on their farms. Assuming a total of 155,000 dairy farmers in the UK,\(^{384}\) the number of observed CJD cases is significantly higher than expected from population estimates. Counting only those farmers with affected cattle, the probability of observing four or more confirmed cases of CJD is estimated at less than one in 10,000.\(^{385}\) In addition, two farmers’ wives were known to have CJD from farms in which clinical BSE had not been reported (although preclinical cases of BSE on these farms might have been expected).


\(^{385}\) Ibid.
5.194 The affected farmers were aged between 54 and 64 and had signs and symptoms typical of sporadic CJD. Two had EEG changes typical of the sporadic disease and all four had type 2 glycosylation patterns. Three farmers were homozygous for methionine at codon 129 and the fourth was a valine homozygote. None conformed to the phenotype characteristic of vCJD. The findings remained unexplained, although a European collaborative study showed a similar increased incidence in deaths due to CJD in farmers in several member states. It was noted that unexpected numbers of affected individuals occurred in other occupational groups, such as the clergy, but numbers in each occupation remained small.

5.195 Among occupational groups exposed to BSE, farmers remain unusual in having such an excess over the incidence of CJD for the population as a whole. No cases of CJD have been reported amount veterinarians exposed to BSE. Four people in the meat industry (butchers, abattoirs, rendering plants, etc) have been reported to have vCJD.\textsuperscript{386} The present evidence has been accepted by some as reassuring in that such occupations may not pose as serious a risk as might have been expected.

\textbf{How many people are likely to succumb to vCJD?}

5.196 The last available figure from the CJDSU before going to press put the total number of definite and probable cases of vCJD at 82, as of 4 September 2000. Of these 69 were confirmed deaths due to vCJD, five were deaths probably due to vCJD, and eight were probable cases of vCJD still alive. The number of patients per year is shown in Figure 5.2 (updated from the 1999 Annual report of the CJDSU). More recently an upward trend has been estimated, showing that deaths have been increasing by 33 percent per year – consistent with an emerging epidemic.\textsuperscript{387} However, due to uncertainty about the length of the incubation period, the routes of infection, genetic susceptibility and resistance, and about the environmental factors which might operate, predictions of the size of the epidemic have encompassed a wide range from a hundred to tens of thousands of individuals. A recent immunohistochemical study\textsuperscript{388} on a random sample of over 3,000 tonsil and appendix specimens has failed to detect any containing PrP\textsuperscript{Sc}. This negative finding gives little comfort as the number of samples tested is relatively small. Furthermore, as the authors of the paper on this study noted, if it is assumed that their test were able to detect infection in the last 75 per cent of the vCJD incubation period, then the upper bound on epidemic size is reduced from several million cases to about 150,000 cases. However, if their tests were only able to detect infection in the last 50 per cent of the incubation period, their results do not reduce the previously reported uncertainty in epidemic size. Therefore, at the time this Report goes to press, it is too early to predict the outcome on the basis of the present number of cases but this will become clearer with time.\textsuperscript{389}

\textsuperscript{386} CJDSU
\textsuperscript{389} An article published on 10 August 2000 suggested the upper limit on the number of cases could be reduced to 136,000: Ghani, A.C., Ferguson, N.M., Donnelly, C.A., Anderson, R.M. (2000) Predicted vCJD mortality in Great Britain, \textit{Nature}, 406, 583–4
Figure 5.2: Cases of vCJD by date of onset, notification, death and confirmation
Annex to Chapter 5:
Information on patients under 50 referred to the CJDSU before 20 March 1996

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