2. History of CJD surveillance up to 1990

Introduction

2.1 This chapter describes the understanding of the epidemiology (the incidence, the distribution and the causes) of CJD in 1990, before the establishment of the CJD Surveillance Unit (CJDSU) in Edinburgh. Work in this area was prompted by action in the USA in the mid-1970s by the United States Department of Agriculture (USDA) to ban the use of meat from sheep and goats exposed to scrapie for human consumption.\(^4\) The ban arose from concerns about the similarities of scrapie to kuru and CJD and the recent transmission of scrapie to primates. Whilst it was felt in Britain that there was no evidence of an increased risk of CJD from exposure to sheep, the USDA action prompted calls for increased research into a disease of substantial economic importance as well as a potential disease of humans. Thus investigation of the causal agents of scrapie in sheep and CJD in man began at the Agricultural Research Council’s (ARC)\(^5\) Institute for Research on Animal Diseases in the late 1970s. Work was also initiated by the Medical Research Council (MRC) following the reported person-to-person transmission of CJD following a surgical transplant procedure in 1974.\(^6\)

2.2 In 1986, when bovine spongiform encephalopathy (BSE) emerged, knowledge derived from this earlier work was already widely available to government and scientists alike. Consequently, concerns about the risk BSE might pose to human health prompted recommendations for further CJD surveillance by both the Southwood Working Party on Bovine Spongiform Encephalopathy (see vol. 4: The Southwood Working Party 1988–89) and the Tyrrell Consultative Committee on Research into Spongiform Encephalopathies (see vol. 11: Scientists after Southwood).

Surveillance in the UK before the emergence of BSE

2.3 The first detailed study of the epidemiology of CJD in the UK was published by Professor Bryan Matthews, University Department of Neurology, Oxford in 1975.\(^7\) Experimental transmission of CJD to primates,\(^8\) and therefore the possibility of natural transmission in humans, prompted this project. Professor Matthews’s study aimed to detect any evidence of natural transmission of CJD and to report on the incidence of CJD in England and Wales between 1964 and 1973. Neuropathologists were asked to notify Professor Matthews of cases of CJD and

---

\(^4\) DMO1 tab 18; S72 Anderson para. 10
\(^5\) Agricultural Research Council – a government-funded Research Council. In 1983, the ARC was renamed the Agricultural and Food Research Council (AFRC) which, in 1994, merged with the Science and Engineering Research Council to become the Biotechnology and Biological Sciences Research Council (BBSRC).
possibly related disorders, which had been verified by histological examination. Information was obtained from hospital notes, questionnaires, and interviews with near relatives.

2.4 Forty-six cases of CJD were identified for the relevant time period, 30 of whom were women and 16 men. The average age of onset was 57 with an age range from 34 to 71. Using the 1971 census figures, the annual incidence of CJD over the period of the study was 0.09 per million.

2.5 The results of the search for sources of natural transmission were largely negative. Two cases were identified that had undergone intracranial surgery (ie, surgery within the skull) and further investigation uncovered ‘strong circumstantial evidence’ of iatrogenic transmission. Another two cases had had some contact with ferrets, and it was known that transmissible mink encephalopathy (TME) was transmissible to ferrets, but this was later thought to be insignificant as none of the ferrets kept by the cases were reported to have TSEs. In addition, two small clusters of cases were detected, one in a small rural community in the Midlands and one in eastern England. Contact between each of the cases in the Midlands could not be established, but further study of the cases in eastern England suggested that iatrogenic transmission or dental procedures might have been involved.

2.6 Professor Matthews concluded that natural transmission from one ‘overt’ case to another case could not account for the occurrence of CJD within the population. He suggested that transmission from non-fatal cases that might remain infective after recovery was a possibility. (There are, however, no known forms of non-fatal CJD.)

Concern about exposure to scrapie and risk of CJD

2.7 In the 1970s, concern was raised by the ARC about the widespread occurrence of scrapie and the similarities between this disease and diseases of the human central nervous system, such as CJD. Further concern about the risks to humans from scrapie arose in 1976 when the US Department of Agriculture decided that the carcasses of sheep and goats affected with, or exposed to, scrapie should not be used for human or animal food.

2.8 These concerns prompted MRC discussions, in 1978, on the value and feasibility of further CJD surveillance, including identification of any increased risk posed by contact with scrapie. As a result of these discussions, an MRC Working Group on CJD was set up later that year chaired by Professor (now Lord) Walton, Professor of Neurology at the University of Newcastle. Other members of this group included Dr Katherine Levy of the MRC and Professor Ingrid Allen,

---

15 S72 Anderson para. 10
16 S5 Martin para. 8
17 YB78/3.9/1.3
18 YB78/10.6/2.1–2.4
Professor of Neuropathology in Queen’s University, Belfast. The MRC Working Group on CJD agreed that retrospective analysis of CJD cases from the period 1970–79 and prospective analysis of CJD cases were important.19

2.9 Consequently, Professor Matthews was awarded several grants between February 1979 and February 1986, in order to conduct the studies discussed and to employ Dr Robert Will as an assistant.20

2.10 The main results from Dr Will’s and Professor Matthews’s work are found in the following three studies:

The retrospective study (1970–79)

2.11 This study involved the analysis of data from Professor Matthews and the Office of Population Censuses and Surveys (OPCS) during the period 1970–79. The main findings were:

i. The study yielded 121 confirmed and 31 probable cases of CJD deaths. The average annual incidence was 0.31 per million.21

ii. One striking finding was the sex ratio of 1.68:1 with 99 female and 59 male cases. The significance of this finding was unknown but a similar ratio was emerging in a case-control study22 being carried out at the time of publication of this study (see paragraph 2.16).

iii. The possibility of case-to-case transmission was investigated by examining the ‘space-time’ clustering of cases. If transmission is occurring in rare diseases, it would be expected that disease onset in cases which are close in space might occur at similar times, provided that the incubation period between infection and disease onset is short. In this study, no significant difference was identified between observed and expected numbers of those dying within 1 to 3 years of each other and within 20 km. However, only the address at the date of onset of disease had been recorded for each case.

iv. It was highlighted that 28 per cent of cases had a past history of major surgery, but no association between these cases could be made which might suggest iatrogenic transmission. However, it was noted that only a case-control study could say if there was an increased risk associated with major surgery and this was not conducted.

v. Occupational data were limited to occupation at date of death with the only noteworthy result being the absence of the disease among farm workers, ie, no increased risk was detected with possible increased exposure to scrapie.

The prospective study (1980–84)

2.12 This study involved identification of CJD cases and comparison of each case with two controls, one with a neurological condition impossible to misdiagnose as
CJD, and the other with a general ‘medical’ complaint. These controls were matched by age, sex and hospital (not community-based controls). Significant findings were:

i. According to the clinical criteria used for diagnosis in the study, there were 83 definite, 32 probable and 25 possible CJD cases identified. The annual incidence of CJD was 0.49 per million. This higher incidence compared to the retrospective study where 0.31 cases per million were observed, was attributed to under-ascertainment in the earlier study.

ii. As with the retrospective study, there was a marked preponderance of females with CJD. This sex difference was significant even allowing for the different age distributions of the female and male populations. However, this finding had not been observed in a similar study carried out in France and again no explanation was offered.

iii. There was no marked difference between CJD patients and controls with respect to surgical history, occupation or animal contact.

2.13 The possibility of carrying out tests for CJD susceptibility in patients was considered during discussions on the design of the prospective study by members of the Working Group on CJD in 1978. For example, it was thought valuable to determine the HLA status of patients. Human Leukocyte Antigens (HLAs) are particular proteins present on the surface of white blood cells, and different types of HLA are associated with specific diseases.

2.14 In the eventuality, it was considered that there was sparse evidence for the involvement of susceptibility factors, and so general genetic screening would not be profitable. Whilst HLA typing was considered important, considerable difficulty was encountered in finding laboratories which were prepared to handle blood samples from CJD patients in view of the potential hazard of infection. Consequently, it does not appear that this work was ever carried out.

Amalgamated study of CJD (1970–84)

2.15 This study was an amalgamation of the data from both of the previous epidemiological investigations to cover the 15 years between 1970 and 1984. Two age-and sex-matched controls were selected for 72 of the 122 cases diagnosed in the period 1980–84. Life histories of places of residence for all subjects were obtained.

2.16 The study identified:

i. 267 patients diagnosed as definite or probable cases of CJD. No evidence of space-time clustering (dates and places of onset) was found.

ii. A relative excess of cases in women was noted again in the age range between 60 and 74 years, although the rates for both sexes appeared similar for those

25 YB78/3.9/1.4; YB78/10.6/2.3
26 YB78/10.6/2.3
people under 60 years of age. The authors were unable to provide an explanation for this observation.

**Human growth hormone-derived CJD**

2.17 The studies described above did not identify an increased risk of CJD with exposure to scrapie nor any evidence of an iatrogenic cause. However, in 1985 it became apparent that several children treated with human growth hormone (hGH) extracted from cadavers in the United Kingdom had later developed CJD. Of 2,000 children treated between 1959 and 1985, approximately 1–1.5 per cent have died from CJD as a result of the treatment. The methods used to prepare the hGH varied over the years, but generally involved maceration of pooled cadaveric pituitary glands in a blender, after storage in acetone. It became apparent that the procedures used had not inactivated the CJD agent.

2.18 The resistance of the scrapie agent to standard disinfection procedures was well documented. Experiments since the late 1950s had shown that it was resistant to treatment with chloroform, phenol, ether, and heating to 100°C. Likewise, the transmission of human spongiform encephalopathies from person to person was well documented in kuru. Thus, it was accepted that the cause of hGH-derived CJD was the inclusion and subsequent failure of inactivation of agent from CJD infected pituitaries. The link between CJD and hGH was considered by the Committee on Safety of Medicines (CSM), of which Dr David Tyrrell was a member, and was the subject of a High Court Action in 1996.

2.19 In December 1995, Dr Robert Milner (Department of Obstetrics, Catholic University of Leuven) put a paper forward to the Spongiform Encephalopathy Advisory Committee (SEAC), proposing that CJD development in recipients of hGH might have been the result of infection with sheep scrapie agent. Evidence for this was derived from reports of the visits by the Medicines Inspectorate to the Pituitary Hormone Laboratory in Cambridge in September 1975 and January 1978. It appeared that equipment used to mince human pituitaries prior to extraction of growth hormone had also been used for the maceration of animal pituitaries potentially exposing the human growth hormone to scrapie agent.

2.20 The theory was considered by SEAC though several difficulties were identified. Firstly, there was no evidence of scrapie ever having crossed the species barrier to humans and secondly, pituitary hormones prepared in other countries where scrapie was not endemic had also caused CJD in recipients. Thus, transmission from a human source remained a more likely explanation for the emergence of these cases. SEAC does not appear, however, to have considered the possibility that CJD could have been transmitted through contaminated animal hormones to cattle. The CJD agent could have contaminated animal pituitaries in

---

28 M2 p. 2
29 Pituitary gland – a small gland found at the base of the brain which produces enzymes that regulate growth and metabolism
30 M2 pp. 25–38
32 Kuru – a human spongiform encephalopathy, found in the Fore people in Papua New Guinea (see vol.2: *Science*); M2, pp. 16–24
34 M2
35 YB96/2.1/1.20
36 YB96/2.1/1.20
the laboratory practices described above. Unfortunately, laboratory inspection reports for the period up to 1975 are no longer available, so it is not possible to ascertain exactly what the procedures used were.

BSE discovery and the recommendations for CJD surveillance

2.21 In December 1986, the Central Veterinary Laboratory (CVL) identified the possible emergence in cattle of a new TSE, later to be known as BSE. In March 1988, in response to a request from the Ministry of Agriculture, Fisheries and Food (MAFF) for advice on the human health risk, the Department of Health (DH) proposed the formation of a Working Party on BSE chaired by Sir Richard Southwood. The remit of the Southwood Working Party was to ‘establish and examine the implications of Bovine Spongiform Encephalopathy (BSE), a newly identified neurological disorder of cattle, in relation to both animal health and any possible human health hazards and to advise the Government on any necessary measures’.

2.22 The membership of the Southwood Working Party reflected its concern with both animal and human health and included Sir John Walton who had chaired the MRC’s Committee on CJD in the 1970s. They met on four occasions between 20 June 1988 and 3 February 1989. (Full details of their deliberations can be found in vol. 4: The Southwood Working Party, 1988–89.)

2.23 The Southwood Working Party discussed the risk that BSE posed to human health. They knew that a link between scrapie in sheep and the human TSE, CJD, had been suggested, but they also knew that there was no evidence to support this suggestion. However, they were aware that the agent causing BSE might be a more ‘virulent’ agent than that causing scrapie, hence the recommendation to destroy carcasses of BSE-affected cattle.

2.24 They considered many points relating to the possible transmission of BSE to humans including:

i. How would it appear and be recognisable?

ii. What risk factors might be involved? Would it be occupationally related, or confined to the food chain only?

iii. What diseases could it mimic, eg, Alzheimer’s, motor neurone disease, and/or multiple sclerosis?

2.25 The Southwood Working Party felt that ‘were transmission to take place then the clinical presentation is likely to be as Creutzfeldt-Jakob Disease’ based on what was known about the neuropathology of BSE. This led them to consider the question of CJD surveillance. They were aware of the studies conducted by

37 See vol. 3: The Early Years, 1986–88
38 IBD1 tab 2 p.3 para. 1.1
39 Now Lord Walton of Detchant
40 S2 Walton para. 4
41 YB88/8.8/4.1
42 YB88/10.27/1.1
Professor Matthews but they queried how sensitive the present surveillance for CJD was and how readily an increase would be detected.

**Southwood recommendations with respect to CJD surveillance**

2.26 On 27 February 1989, the Working Party report was published including their comments on CJD surveillance. The report discussed in detail the possible transmission of BSE to man. It commented that humans were susceptible to some spongiform encephalopathies but that close examination of the evidence suggested that:

> It is likely that cattle will prove to be a ‘dead-end host’ for the disease agent and most unlikely that BSE will have any implications for human health.

2.27 However, the Report also stated that it would be a decade or more before complete reassurance of an absence of risk to humans could be given, because of the very long incubation period of TSEs in humans.

2.28 The Southwood Working Party expressed the view, in paragraph 5.3.6 of their report, that:

> It is a reasonable assumption that were BSE to be transmitted to humans, the clinical disorder would closely resemble CJD. Depending upon the route of transmission, the incubation period could be as little as a year (as with some iatrogenic CJD cases) or several decades (as estimated for many natural CJD cases). Identification of any such cases as unusual or atypical would not be easy. However, the Chief Medical Officer could consider whether specialist branches of the medical profession such as neurologists, neurophysiologists and neuropathologists, to whom cases of suspected CJD are referred for diagnosis, should be made aware of the emergence of BSE so that they can report any atypical cases or changing patterns in the incidence of disease. CJD also remains of considerable interest to epidemiologists and they should also be advised to watch for any changing patterns in relation to the disease. The Office of Population Censuses and Surveys is already reviewing deaths attributed to CJD and will be looking for any trend or particular occupation or other characteristics in the deaths certificated to CJD. The question of specific monitoring of population groups considered at enhanced risk of BSE exposure, or more detailed surveys of CJD cases, are included amongst those to be referred to the Consultative Committee on Research.

43 YB88/5.19/2.17

44 YB88/5.19/2.19


46 IBD1 tab 2 para. 5.3

47 IBD1 tab 2 para. 9.2

48 IBD1 tab 2 para. 5.3.1

49 IBD1 tab 2 para. 5.3.6
Government’s response to Southwood recommendations with respect to CJD surveillance

2.29 MAFF and DH announced their response to the *Southwood Report* on the same day as it was published.\(^{50}\) This response included the statement that the Chief Medical Officer (CMO) was ensuring that mechanisms were in place to detect any change in the pattern of CJD, and announced that the Departments intended to set up a Consultative Committee on Research into Spongiform Encephalopathies.

2.30 The CMO, Sir Donald Acheson, wrote on 24 February 1989 to the President of the Association of British Neurologists, Professor David Shaw, enclosing a copy of the *Southwood Report*. He stated that he would be asking all the neurologists and neurophysiologists for their assistance in monitoring any changes in TSE patterns in man. He also said that the new Consultative Committee on Research, under the chairmanship of Dr David Tyrrell,\(^{51}\) would be considering whether more formal monitoring of CJD cases would be appropriate.\(^{52}\) Professor Shaw responded on 1 March 1989, offering the cooperation of the Association of British Neurologists.\(^{53}\)

2.31 On 2 March 1989, Dr Hilary Pickles, Department of Health (DH) secretary to the Southwood Working Party, minuted Sir Donald asking for a steer on a letter she was drafting on his behalf to neurologists and neurophysiologists. In particular, she sought his advice about what neurologists should do in terms of reporting if they believed they had identified an atypical case of CJD. Dr Pickles suggested four options for monitoring any changes reported by neurologists: the Office of Population Censuses and Surveys; the Communicable Disease Surveillance Centre (CDSC);\(^{54}\) DH; and an MRC-coordinated surveillance study similar to Professor Matthews’s study ten years previously.\(^{55}\) She proposed that the ‘most satisfactory solution’ would be an MRC-coordinated study. Her minute included a handwritten note stating that:

> Since writing this I have spoken to Dr Will the neurologist who was involved in the earlier monitoring exercise with CJD and who is on the Tyrrell Committee. He is firmly convinced that only a proper study, with an experienced neurologist deciding which cases can be accepted as true CJD, will give us the information we need. Clinical diagnosis and death certification is potentially misleading in his view.

2.32 Both Sir Donald and Professor Shaw agreed with Dr Pickles that the best way forward for the CJD monitoring was to continue with the system of notification that Professor Matthews had previously instituted.\(^{56}\) DH also agreed that until the matter of CJD surveillance was discussed with the Tyrrell Consultative Committee on Research and the MRC, the CMO would postpone writing to the neurological network.\(^{57}\)

2.33 Sir Donald, in a letter to Professor Shaw, suggested that the reinstitution of surveillance would be a relatively straightforward task, especially as Dr Will, who
was a consultant neurologist with experience of working with Professor Matthews
on CJD surveillance, was to be included on the Tyrrell Committee, which was to
discuss the plans for CJD surveillance:

Would the best way to ensure a continuation of the surveillance of CJD be
to invite Dr Will simply to take up Bryan Matthews’s mantle if this has not
already been passed on to someone else and leave it at that?\textsuperscript{58}

2.34 However, Professor Matthews soon highlighted to Professor Shaw the
problems that would be encountered in the surveillance of CJD (see paragraphs
2.11–2.16).\textsuperscript{59} Professor Shaw then passed on these comments to Sir Donald.\textsuperscript{60} In
summary:

i. It was essential that supposed cases were seen by someone (perhaps more than
once) with clinical experience.

ii. Reliance on death certificates was no help, as ‘CJD is written on death
certificates in quite a reckless way!’

iii. The necessary chasing of pathologists for reports could take up much time.
Pathologists were reluctant to perform post-mortems and would be more so after
reports of CJD in three neuropathology technicians. There was also the related
expense of getting the bodies to willing pathologists.

iv. There were potential difficulties in employing a research registrar to do the
leg-work for Dr Will. Research registrars would normally expect to produce
publications from their work at this stage in their career and this work might not
be original enough as several papers had already been written on CJD
surveillance.

v. A large budget would be needed to maintain the surveillance for a sufficient
period of time, taking into account the long incubation period of human TSEs.

2.35 Sir Donald and Professor Shaw discussed these difficulties and sought advice
from Dr Will.\textsuperscript{61} The final outcome of their request for advice was that Dr Will
presented a paper on his proposals for CJD surveillance at a meeting of the Tyrrell
Committee (see below).

\textbf{Tyrrell recommendations with respect to CJD surveillance}

2.36 The Tyrrell Committee met in March, April and May of 1989. The members
of this Committee who had experience of CJD surveillance were Dr Tyrrell, the
Chairman, and Dr Will.

2.37 Dr Tyrrell had been a member of the Committee on Safety of Medicines
(CSM) when it had considered the problems of CJD induced by human growth
hormone (see paragraphs 2.17–2.18). He also served as Chairman of the Advisory
Committee on Dangerous Pathogens (ACDP), which recommended safe working
practices in laboratories handling, amongst other things, TSEs.\textsuperscript{62} (See vol. 6:
\textit{Human Health, 1989–96} for more details on the ACDP.)

\begin{footnotes}
\item[58] YB89/3.7/1.1
\item[59] YB89/3.23/3.1
\item[60] YB89/4.24/7.1
\item[61] YB89/4.27/7.1
\item[62] S11 Tyrrell para. 5
\end{footnotes}
2.38 Dr Will was a consultant neurologist at the Western General Hospital in Edinburgh. Between November 1979 and January 1982, he had worked with Professor Matthews on the surveillance of CJD both in England and Wales.63

2.39 CJD surveillance was discussed at all three meetings of the Tyrrell Committee, and Dr Will presented a paper entitled ‘Proposal for the Monitoring of Creutzfeldt-Jakob Disease’64 at the second meeting in April 1989.65 Monitoring the incidence of CJD in humans, and instigating a study of relevant occupational groups such as abattoir workers, were suggested but it was also noted that the clinical features of BSE in humans might prove different from sporadic CJD, as had some of the iatrogenic CJD cases.66

2.40 The Committee approved the proposals in Dr Will’s paper and agreed that a surveillance programme should cover all of Britain. It was noted that the programme duration was expected to be lengthy, as it was known that possible analogous human diseases such as kuru had long incubation periods.67

2.41 The Tyrrell Report was presented to the Government on 10 June 1989. Dr Pickles urged her colleagues in DH to arrange the funding for the CJD surveillance programme quickly. She felt that DH should be seen to have research ‘on the road’ when the Tyrrell Report was finally published and that this programme was the most urgent project for DH.68

2.42 On 9 January 1990, the Tyrrell Report was finally published. The Report recommended the monitoring of all UK cases of CJD over the following two decades. It reiterated the view that scrapie was not considered causally linked with CJD but that it was ‘urgent that the same reassurance can be given about the lack of effect of BSE on human health.’69

2.43 The Report separated the CJD surveillance project into two parts:70

i. Surveillance of cases of CJD with particular reference to the overall incidence, the geographical distribution, the age and sex distribution, occupational history, association with medication, and any atypical clinical features. This part of the project was rated the highest priority.

ii. Prospective monitoring of groups with high exposure to bovine tissues, such as slaughtermen, veterinarians, and regular recipients of medicinal products of bovine origin. This part of the project was rated the lowest priority. As described in subsequent chapters of this volume, this monitoring was not in the event undertaken, as it was considered that the same result could be obtained from an analysis of the occupations of CJD cases.

63 T6 p. 12
64 YB89/5.00/5.1
65 YB89/4.11/2.2–2.3
66 YB89/4.11/2.2
67 S11 Tyrrell para. 18
68 YB89/9.6/4.1; YB89/9.7/3.1; YB89/12.12/2.1
69 IBD1 tab 4 p. 10
70 IBD1 tab 4 p. 11