4. Work of the CJD Surveillance Unit

Introduction

4.1 This chapter describes the work of the CJDSU from its establishment in 1990 to the announcement of a possible link between BSE and a new variant of CJD on 20 March 1996. The studies conducted by the CJDSU are described below, with attention being paid to the development of the questionnaire used to obtain clinical and epidemiological information, along with the results obtained from these studies. The work which led to the identification of a new variant of CJD is described in detail in the next chapter.

Retrospective study of CJD

4.2 Although there had been epidemiological studies of CJD carried out between 1970 and 1984 in both England and Wales, these studies had not been extended beyond 1984. The CJDSU’s first task was therefore to fill this gap in epidemiological data and include data from Northern Ireland and Scotland.

4.3 Information for the retrospective analysis came from death certificates provided by the Office of Population Censuses and Surveys (OPCS) and equivalent bodies in Northern Ireland and Scotland. Direct referral of cases from neuropathologists, neurologists and electrophysiologists was also encouraged. A total of 260 suspect cases of CJD were ascertained in this study. Hospital records were obtained for all these cases, but no questionnaires were used. These suspect cases were then classified using criteria based on those established by Masters et al. in 1979 (see paragraph 3.12 for a description of the criteria).

4.4 The overall incidence over the period studied, 1985 to 1990, was 0.46 per million per annum, which was consistent with the 1980–84 survey of CJD in the UK.

4.5 The clinical features of CJD in this survey were also analysed. This was an important aspect of the survey as it was believed that if BSE was transmitted to humans it might present itself in a different manner to that previously seen in CJD. The frequency of clinical features such as myoclonus (muscle spasms), pyramidal signs (abnormal reflexes) and akinetic mutism (impairment of voluntary movement) were comparable to the previous investigations.

147 IBD2 tab 4 p. 1
Prospective study of CJD

4.6 The other major task was to establish a system for the prospective surveillance of CJD that would be able to detect any changes in epidemiology or clinical characteristics, as a result of the emergence of BSE.\textsuperscript{149} The main epidemiological parameters investigated included number of cases, geographical distribution of cases and occupational incidence.

4.7 Primarily, this was achieved by direct referral of any suspect cases of CJD through the neurological network, comprising neurologists, neurophysiologists and neuropathologists. These professionals were also asked to report all cases of subacute dementing illnesses or progressive cerebellar dysfunction in specific occupational groups (veterinarians, herdsmen, slaughtermen, farmers, butchers and laboratory workers).\textsuperscript{150} However, as a precaution, all death certificates mentioning CJD were also obtained from the OPCS, and equivalent bodies in Scotland and Northern Ireland, and assessed.\textsuperscript{151}

4.8 Another proposal for improving ascertainment was that CJD should be made a notifiable disease. This was put forward during evidence to the Agriculture Select Committee’s inquiry into BSE which reported in July 1990, but it was not supported by either the CMO or Dr Will.\textsuperscript{152} In order to make CJD a notifiable disease, specific diagnostic criteria, which cases would have to fulfil, would have to be established. Dr Will believed that some cases might then be missed as there might be a reluctance to notify cases that did not fulfil the criteria absolutely. In addition, the necessary diagnostic criteria could only be used in the later stages of disease and that might result in cases being missed.\textsuperscript{153}

4.9 Dr Will’s opinion was supported by the EU Surveillance Group in 1994 and recent data from this Group has revealed that making CJD a notifiable disease was not likely to improve case ascertainment but might actually be detrimental. For example, the introduction of notification in Slovakia has been stated to have resulted in a decrease in the number of referrals.\textsuperscript{154}

4.10 Each patient referred to the CJDSU was visited in order to verify the diagnosis and obtain the relevant information.\textsuperscript{155} The clinical and epidemiological information was obtained by a standard questionnaire. Because of the rapid progress of the illness, this could not be answered by the patient but instead was answered by the relatives of the patient.

4.11 After obtaining this information, the CJDSU compared the retrospective and prospective data in an attempt to reveal any change in either the epidemiology or the clinical characteristics of CJD.\textsuperscript{156}

\textsuperscript{149} YB89/12.5/1.1
\textsuperscript{150} YB89/12.5/1.8
\textsuperscript{151} YB89/12.5/1.7
\textsuperscript{152} IBD1 tab 7 p. xii
\textsuperscript{153} IBD1 tab 7 p. 86
\textsuperscript{154} S61 Will para. 25
\textsuperscript{155} IBD2 tab 4 p. 7
\textsuperscript{156} YB89/12.5/1.1
Development of the questionnaire

4.12 The questionnaire used by the CJDSU was based on the previous one developed by Dr Will in 1979 for his work with Professor Matthews. It included sections on patient’s symptoms just prior to becoming ill (prodromal phase), past medical history, family history, social history (residential, occupation, diet), exposure to animals, clinical history, results of diagnostic investigation and case classification.

4.13 Minor changes were made to it before it was used in 1991 and subsequent alterations were made throughout the period 1991–95, as knowledge about CJD developed. After the identification of the variant form of CJD in 1996 and the possible link between this new form of CJD and BSE, substantial changes were made to the questionnaire, in an attempt to discover if indeed there was a causal link (see Annex 1 for the latest version). Table 4.1, below, describes the changes made.

Development of the statistical analysis – epidemiology

4.14 The results of the questionnaire provided information to the CJDSU on variables such as sex, age, incidence, and geographical distribution of cases. Dr (now Professor) Peter Smith of the Department of Epidemiology, London School of Hygiene and Tropical Medicine, who had been involved in previous CJD studies, conducted the statistical analysis of temporal changes in these variables.

Results of the surveillance (1991–95)

4.15 The CJDSU summarised its progress and findings in a series of annual reports. The topics covered by these reports were clinical surveillance of CJD, neuropathological validation of diagnosis, genetic studies, European surveillance, collaborative work and committee membership.
Table 4.1: Development of the CJD questionnaire

<table>
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<tr>
<td>Additional question on whether the patients had gained weight prior to visiting the doctor.</td>
<td>Additional question on whether the patient had ever had an organ transplant.</td>
<td>Question on whether the patient had ever undergone operations involving stitching; or neurological, ear, abdominal, orthopaedic surgery, tonsillectomy and appendectomy.</td>
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<td>Past medical history</td>
<td>Additional question to find out if the patient had ever been tested for glaucoma.</td>
<td>Rewording of contact with person question to include contact with any person with a serious dementing illness.</td>
<td>Question on whether the patient had received albumin or immunoglobulin transfusions.</td>
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<td>More detailed questions on medication under different medicine headings: prescribed, over-the-counter purchases, homeopathic, herbal, eyedrops.</td>
<td>Further questions on other conditions: shingles; herpes/simpex; rheumatoid arthritis; diabetes melitus, and allergies.</td>
<td>Question on whether the patient had been subjected to lumbar puncture or electrical tests involving needles.</td>
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<tr>
<td>Additional questions on vaccination, tattooing, ear piercing and acupuncture.</td>
<td>Additional question on the use of hormone supplements.</td>
<td>Question on the use of recreational drugs more detailed.</td>
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<td>Questions on asthma and skin sensitivities removed.</td>
<td>Additional question on whether the patient had ever had an electromyograph (EMG).</td>
<td>Questions on clinical and pathological investigations carried out on the patient during the illness.</td>
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<td>Family history</td>
<td>Questions on eating habits expanded to cover lamb/mutton, pork/bacon/ham, beef, venison, veal, poultry and fish; sausages, liver, kidneys, sweetbreads, tongue, brains, trotters, puddings, eyes, haggis and heart; rare or undercooked meats; dairy products.</td>
<td>Eating section divided into two time frames: ever consumed or product consumed after 1985?</td>
<td>Eating section limited to one time frame, since 1980.</td>
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<tr>
<td>Additional question on contact with fertiliser, bone meal, hoof and horn and dried blood.</td>
<td>Questions on shellfish, raw fish, beefburgers, milk and cheese.</td>
<td>Additional questions on school dinners; eating of animal food or pet food; cutting of raw red meat or bones at work or home.</td>
<td></td>
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<tr>
<td>Social history (residential, occupation, diet)</td>
<td>Eating section limited to one time frame, since 1980.</td>
<td>Question on eating faggots and steak tartare.</td>
<td>Question on eating faggots and steak tartare.</td>
</tr>
<tr>
<td>Exposed to animals</td>
<td>Added question on contact with cats, sheep and deer.</td>
<td>More specific questions on occupational history.</td>
<td>More specific questions on occupational history.</td>
</tr>
<tr>
<td>Case-control analysis</td>
<td>Questionnaire issued to one control subject not two. Matched for same hospital, sex and age.</td>
<td>Added question on contact with horses, pigs, fur animals, rodents and hamsters, and date of first exposure.</td>
<td>Four community-based controls instead of hospital-based controls.</td>
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<td>Four community-based controls instead of hospital-based controls.</td>
<td>Added question on animal bites.</td>
<td>Question on treating cattle for warble fly; dipping sheep; crop spraying.</td>
<td>Question on treating cattle for warble fly; dipping sheep; crop spraying.</td>
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Clinical surveillance

4.16 The results of the retrospective survey (1985–90) and the first five years of the prospective study, up to April 1995, showed an increase in incidence since 1990 (see Table 4.2, below) but this was thought to be due to improved case identification, referral and diagnosis. There was also no evidence of any change in geographical distribution of CJD.

Table 4.2: Deaths from Creutzfeldt-Jakob Disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Total deaths</th>
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<tbody>
<tr>
<td>1985</td>
<td>28</td>
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<tr>
<td>1986</td>
<td>26</td>
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<tr>
<td>1987</td>
<td>24</td>
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<td>1988</td>
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<td>36</td>
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<td>1992</td>
<td>51</td>
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<td>1993</td>
<td>42</td>
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<tr>
<td>1994</td>
<td>55</td>
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<tr>
<td>1995 (to 30 April)</td>
<td>8</td>
</tr>
</tbody>
</table>

4.17 No comment was made about sex ratio, although in the earlier studies up to 1984, a higher preponderance of females developing CJD had been detected. Each report concluded that there was no evidence to suggest a change in the epidemiological characteristics of CJD following the arrival of BSE.

4.18 No change in the clinical features was detected. The importance of the analysis of the clinical presentation and features of each case was emphasised. CJD presented with a range of clinical signs. Human growth hormone recipients who subsequently developed CJD almost always presented with ataxia, problems with the control of muscle tone and balance; with cognitive impairment, disorders in thought processes, developing late in the course of the disease, if at all. However, iatrogenic cases caused by neurosurgical cross-contamination, and sporadic cases of CJD, presented with a progressive cortical dysfunction including dementia.

4.19 It was felt that differences in the ‘route of inoculation was the likeliest explanation for these disparate clinical features’ and that this was ‘potentially of relevance to assessing the risk of Bovine Spongiform Encephalopathy (BSE) as any theoretical contamination of the human population would be more likely by a peripheral route’. Therefore the CJDSU felt that if BSE caused disease in the human population it would present with similar clinical features to iatrogenic CJD caused by human growth hormone (hGH), where the patients were also affected through a peripheral route of inoculation.

4.20 Hence the CJDSU had studied the proportion of cases of CJD with ataxia as the predominant presentation. The reported findings highlighted the fact that the
number of cases with this presentation was very low, was not seen to be increasing in proportion to the total number of cases, and was thus consistent with the findings of studies carried out before the emergence of BSE.

**Case-control analysis**

4.21 The case-control analysis of dietary history suggested in one annual analysis an association with consumption of white pudding or black pudding, in another an association with veal consumption, and in another an association between venison consumption and an increased risk of CJD. However, the data behind these associations were thought to be tenuous and were later shown not to be significant. It was also noted that there was no overall ‘statistical evidence of an association between consumption of a variety of animal-products post-1985 and risk of CJD’.

4.22 Results from the analysis of occupational history and risk of CJD provided no evidence that CJD cases were more likely than controls to have been exposed to TSEs. However, reference was made to the three cases of CJD in farmers (see chapter 5). The report emphasised that, in each of these three cases, the clinicopathological features were compatible with sporadic CJD and ‘no mechanism of cross-contamination [had] been identified in any of these cases’. In addition, the relative risk in farmers in other countries in Europe, which were either BSE-free or had only a very small number of cases, was similar to that of farmers in the UK.

**Neuropathological validation**

4.23 In May 1991, the CJD Neuropathology Surveillance project was established, under the direction of the neuropathologist, Dr Jeanne Bell. The aims of the project were ‘to map the distribution of the abnormal prion protein within the central nervous system of affected individuals; to investigate the associated tissue damage and cellular reactions; and to correlate these with the clinicopathological findings’.

4.24 The laboratory obtained autopsy and occasional biopsy material from local cases and from collaborating pathologists throughout the UK. All samples were examined neuropathologically for the presence of the abnormal prion protein to confirm, or not, CJD. Diagnostic reports were then sent to the referring neurologists.

4.25 Complementary research was also undertaken, looking at new diagnostic techniques to locate the prion protein and relating prion protein deposition to other features of the disease, such as clinical features and prion protein genotype.
Genetic studies

4.26 This covered the analysis of DNA from blood from suspect CJD cases to screen for mutations of the prion protein gene. Initially, this work was conducted by Dr (now Professor) John Collinge’s group at St Mary’s Hospital, London, but after 1992, CJDSU conducted the genetic analysis in Edinburgh with the assistance of the Centre for Genome Research.\textsuperscript{172}

4.27 By the time the Third Annual Report was written in September 1994, 120 DNA samples from blood had been analysed and nine mutations of the PrP gene had been identified.\textsuperscript{173} This gave a reported figure for familial CJD of 13.4 per cent of total cases. This represented an approximate doubling in the identification of cases presumed to be familial in the years 1990 to 1993, compared with the retrospective study, which covered the period 1980 to 1984. This increase was thought to be due to the improved molecular and biological techniques used for diagnosis. (See vol. 2: \textit{Science} for an up-to-date list of genetic mutations associated with familial CJD.)

4.28 Much of the work on genetic studies had centred on the genotype at codon 129 of the prion protein gene. By 30 April 1994, the genotype at codon 129 had been analysed in 117 sporadic cases of CJD.\textsuperscript{174}

4.29 There is a variable genotype at codon 129 in the normal population (see vol. 2: \textit{Science}). In contrast to the mutations of the prion gene described above which are linked with familial CJD, this polymorphism at codon 129 is not the cause of sporadic CJD but appears to be associated with susceptibility to CJD. This increased risk is linked to homozygosity at codon 129,\textsuperscript{175} which has been shown to occur more frequently in CJD patients than in the general population. An excess of methionine homozygotes was detected in sporadic CJD and in cases of iatrogenic CJD due to neurosurgical cross-contamination (a central route of inoculation). In iatrogenic CJD caused by human growth hormone (hGH) (a peripheral route of inoculation), an excess of homozygotes was detected again but in this group there was a relative excess of valine homozygotes. The report suggests that:

A plausible explanation for this finding is that the genotype influences the likelihood of developing CJD in relation to the route of inoculation. The theoretical transmission of BSE to the human population would be more likely by a peripheral route of inoculation. If this occurred evidence supporting it may come from the clinical presentation and from serially analysing the codon 129 genotype of sporadic cases of CJD in order to determine whether there is an increase in the proportion of valine homozygotes with time. There is currently no evidence of such a change.\textsuperscript{176}

(In the eventuality, cases of variant CJD have been shown to be methionine homozygotes. Analysis of the genotype at codon 129, however, is not a diagnostic test, but is of interest in relation to susceptibility factors. The fact that previous experience suggested that victims of CJD of a BSE origin might be valine homozygotes, is therefore not important.)

\textsuperscript{172} IBDD tab 8 pp. 27–8
\textsuperscript{173} IBDD tab 8 pp. 2 and 8
\textsuperscript{174} IBDD tab 8 p.27
\textsuperscript{175} In human cells, two copies of each gene are present, one derived from each parent. Where both copies of the genes are identical, an individual is termed homozygous for that gene. In this case, homozygosity at codon 129 refers to the fact that both gene copies are identical at codon 129
\textsuperscript{176} IBDD tab 6 p. 8
4.30 There was no section covering the genetic studies of the CJDSU in the Fourth Annual Report, so the findings above are based on data up to 30 April 1994 in the Third Annual Report.

4.31 In 1996, the results from a collaborative study between Dr Collinge’s group, the CJDSU and the Centre for Genome Research at the University of Edinburgh found that sporadic cases tend to be homozygous for either methionine or valine.\textsuperscript{177} However, a recent study of 300 cases of sporadic CJD has found some cases which are heterozygotes at codon 129.\textsuperscript{178}

**European surveillance**

4.32 The CJDSU Second Annual Report noted the award of a grant, by the European BIOMED 1 programme, in 1993, to Dr Will and Professor Albert Hofman of Erasmus University, Rotterdam. This funding was provided to coordinate Europe-wide surveillance of CJD.\textsuperscript{179} This project was important in relation to the UK study, as a comparison of the epidemiological characteristics of CJD in the UK with those in other European countries would highlight any changes in CJD in the UK as a result of the emergence of BSE.

4.33 It was reported in the 1994 Third Annual Report, that no significant difference in the incidence of CJD between the participating countries was found.\textsuperscript{180} These findings had been published earlier in 1994 in a letter to *The Lancet*.\textsuperscript{181} The Annual Report also noted that the case-control aspect of the European project would provide invaluable comparative information on the risk factors for CJD and would put any positive findings from any individual country (including the UK) in context.

**Fifth Annual Report (1996)**

4.34 This was finally published on 15 September 1997 and covered the period up to the end of April 1996. The delay in publication was due to the increased workload of the CJDSU as a result of the identification of a new variant form of CJD and the possible link between this and BSE.

4.35 The work of the CJDSU from May 1995 is covered in Chapter 5.


\textsuperscript{179} IBD2 tab 6 p. 9

\textsuperscript{180} IBD2 tab 8 p. 28