Seventh Annual Report 1998

Creutzfeldt-Jakob Disease Surveillance in the UK

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SECTION 1

Summary

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. The information provided in this seventh report continues to provide evidence of a high level of case ascertainment and that detailed clinical and epidemiological information has been obtained for the great majority of patients. A high post mortem rate has been maintained through the period of the study 1990-1998. The success of the project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

The average number of cases of sporadic CJD identified annually since 1990 was higher than in previous surveillance periods extending back to 1970. It is impossible to say with certainty to what extent these changes reflect an improvement in case ascertainment and to what extent, if any, changes in incidence.

In England, Scotland and Wales mortality rates from sporadic CJD were, respectively, 0.68, 0.74 and 1.03/million/year. These rates are comparable to those observed in other countries in Europe and elsewhere in the world, including countries which are free of BSE. Mortality from sporadic CJD in Northern Ireland was lower (0.34/million/year). This difference is not statistically significant. There was some variation in the rates between the different regions within Great Britain but this variation is not statistically significant. The highest mortality from sporadic CJD was observed in the South-West region of England (SMR=126 [compared to 144 in the last report]). Previous analyses have found no convincing evidence of space-time clustering, and this remains the case for the analyses in this report.

A case-control analysis of medical risk factors in sporadic CJD has not provided evidence that any putative medical risk factor is actually associated with an increased risk of CJD. Risk factors analysed include a past history of any surgery, a history of neurological or eye surgery, a history of organ transplantation or blood transfusion or a history of regular GP or out-patient attendance. Neither was there evidence that acupuncture, tattooing or ear/body piercing is associated with increased risk of CJD. A family history of dementia was reported in significantly more cases than controls.

Up until 31 December 1998, there have been 35 deaths from new variant CJD (nvCJD) in the UK and in 33 of these cases the diagnosis has been confirmed neuropathologically. The clinical and neuropathological features of all these cases of nvCJD are remarkably uniform and consistent with previous descriptions[1,2,3]. Statistical analysis has provided no evidence of space-time clustering of cases of nvCJD nor that the rate of occurrence of new cases has increased with time since 1994. Risk factors for the development of nvCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - 33 cases of nvCJD with available genetic analysis have all been methionine homozygotes. The analyses in this report do not provide evidence to suggest that there is an increased risk of nvCJD through past surgery, previous blood transfusion, occupation or a range of dietary factors. However, the power of the case-control study is limited by the small number of cases and controls. For some putative risk factors, such as blood transfusion or surgery, it will be many years before an accurate assessment of risk can be made because of the likely prolonged incubation periods.

[1] Zeidler M, Johnstone EC, Bamber RWK, Dickens CM, Fisher CJ, Francis AF, Goldbeck R, Higgo R, Johnson-Sabine EC, Lodge GJ, McGarry P, Mitchell S, Tarlo L, Turner M, Ryley P, Will RG. New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 1997; 350: 908-910.

[2] Zeidler M, Stewart GE, Barraclough CR, Bateman DE, Bates D, Burn DJ, Colchester AC, Durward W, Fletcher NA, Hawkins SA, Mackenzie JM, Will RG. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet 1997; 350: 903-907.

[3] Ironside JW. New-variant Creutzfeldt-Jakob disease. Neuropathology 1998; 18(2): 131-138.

SECTION 2

2. Clinical Surveillance

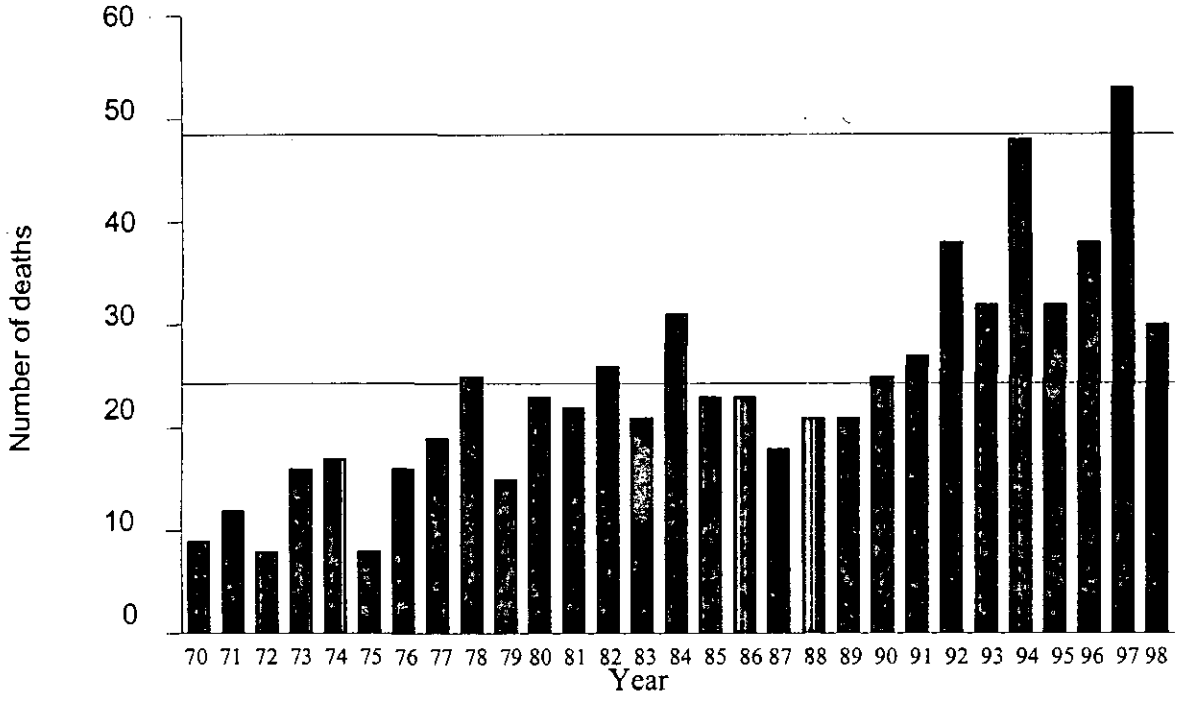
The national surveillance of CJD was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Office Department of Health. The initial aim of the project was to identify any change in the pattern of CJD that might be attributable to the emergence of bovine spongiform encephalopathy (BSE). Following the occurrence of nvCJD the project now aims to monitor the characteristics of all forms of CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings from the CJD Surveillance Unit in relation to sporadic, familial, iatrogenic and new variant CJD up to 31st December 1998.

2.1 Sporadic Creutzfeldt-Jakob disease

Between 1st January 1970 and 31st December 1998, 758 cases of sporadic CJD were identified, of whom 3 cases were still alive on 31st December. Of these, 596 (79%) were classified as definite cases with the remainder classed as probable. Figure 1a shows the number of deaths each year from sporadic CJD for England and Wales between 1970 and 1998 and Figure 1b shows similar data for Scotland and Northern Ireland between 1985 and 1998. In England and Wales the number of deaths identified each year has increased from an average of about 10 per year at the beginning of the 1970s, to about 35 per year in the 1990s. No secular trend is apparent over the shorter time period for which data are available for Scotland and Northern Ireland. Over the period 1990-1998 the average annual mortality rates from sporadic CJD per million population were 0.68 in England, 1.03 in Wales, 0.74 in Scotland and 0.34 in Northern Ireland, as shown in Table 1. When account is taken of age and sex,

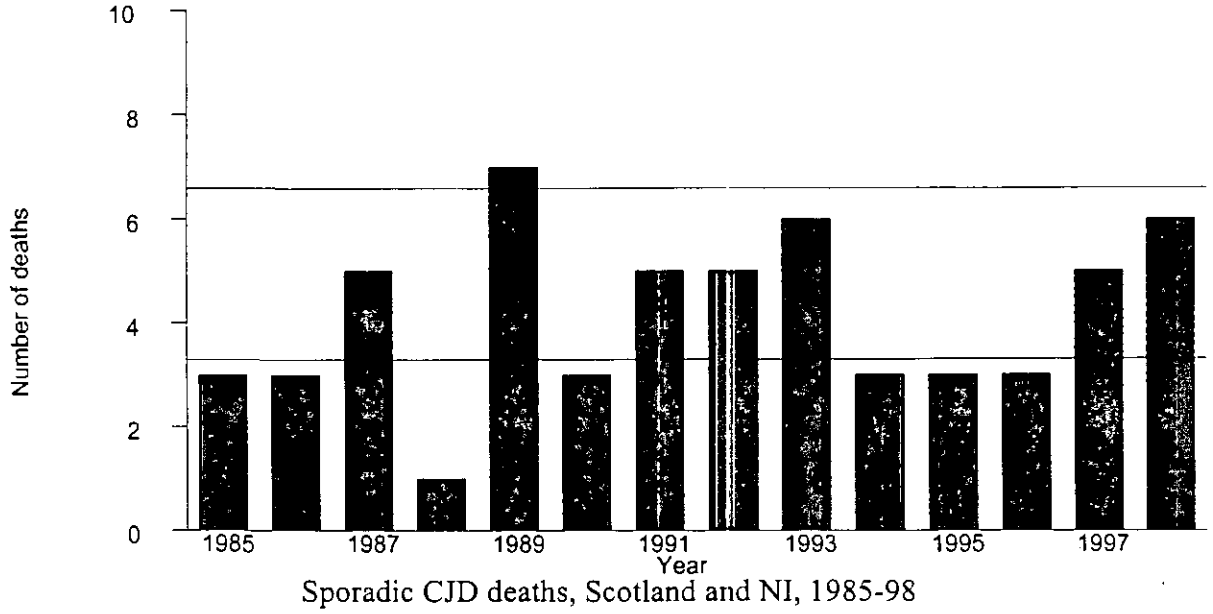
the variation in recorded mortality between the different countries is not statistically significant (p = 0.2).

Figure 1a Deaths from sporadic CJD, England and Wales, 1970-1998



Sporadic CJD deaths, England and Wales, 1970-98

Figure 1b Deaths from sporadic CJD, Scotland and Northern Ireland, 1985-1998



Sporadic CJD deaths, Scotland and NI, 1985-98

Note: the horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year

Table 1 Deaths from sporadic CJD by region and country 1990-1998

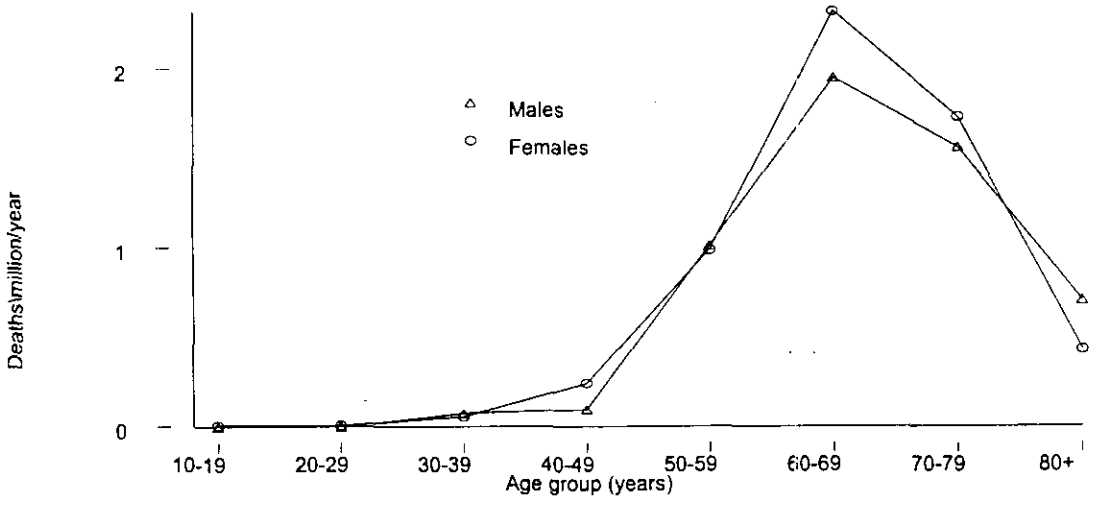
	No of cases	Total no (incidence /annum)
ENGLAND		
North		
Cleveland	0	
Cumbria	8	
Durham	4	21 (0.75)
Northumberland	2	
Tyne & Wear	7	
East Midlands		
Derbyshire	4	
Leicestershire	5	
Lincolnshire	2	16 (0.43)
Northamptonshire	2	
Nottinghamshire	3	
South East		
Bedfordshire	4	
Berkshire	6	
Buckinghamshire	1	
East Sussex	6	
Essex	11	
Greater London	38	
Hampshire	6	100 (0.62)
Hertfordshire	4	
Isle of Wight	1	
Kent	8	
Oxfordshire	4	
Surrey	4	
West Sussex	7	
North West		
Cheshire	6	
Greater Manchester	14	42 (0.73)
Lancashire	9	
Merseyside	13	
WALES		
Clywd	3	
Dyfed	2	
Gwent	4	
Gwynedd	6	
Mid Glamorgan	4	
Powys	2	
South Glamorgan	2	
West Glamorgan	4	
TOTAL FOR WALES		**27 (1.03)**
NORTHERN IRELAND	5	**5 (0.34)**

	No of cases	Total no (incidence/ annum)
ENGLAND		
Yorkshire & Humberside		
Humberside	3	
North Yorkshire	7	27 (0.60)
South Yorkshire	6	
West Yorkshire	11	
East Anglia		
Cambridgeshire	3	
Norfolk	6	17 (0.90)
Suffolk	8	
South West		
Avon	8	
Cornwall	3	
Devon	9	
Dorset	8	43 (1.00)
Gloucestershire	4	
Somerset	5	
Wiltshire	6	
West Midlands		
Hereford & Worcs.	2	
Shropshire	2	
Staffordshire	3	25 (0.52)
Warwickshire	1	
West Mids (Met)	17	
TOTAL FOR ENGLAND		**296* (0.68)**
SCOTLAND		
Borders	0	
Central	2	
Dumfries & Galloway	0	
Fife	2	
Grampian	5	
Highland	1	
Lothian	8	
Strathclyde	14	
Tayside	1	
Islands (Shetland)	1	
Islands (Orkney)	0	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**34 (0.74)**

* Exact residential history is not available in 5 cases and therefore county cannot be allocated.

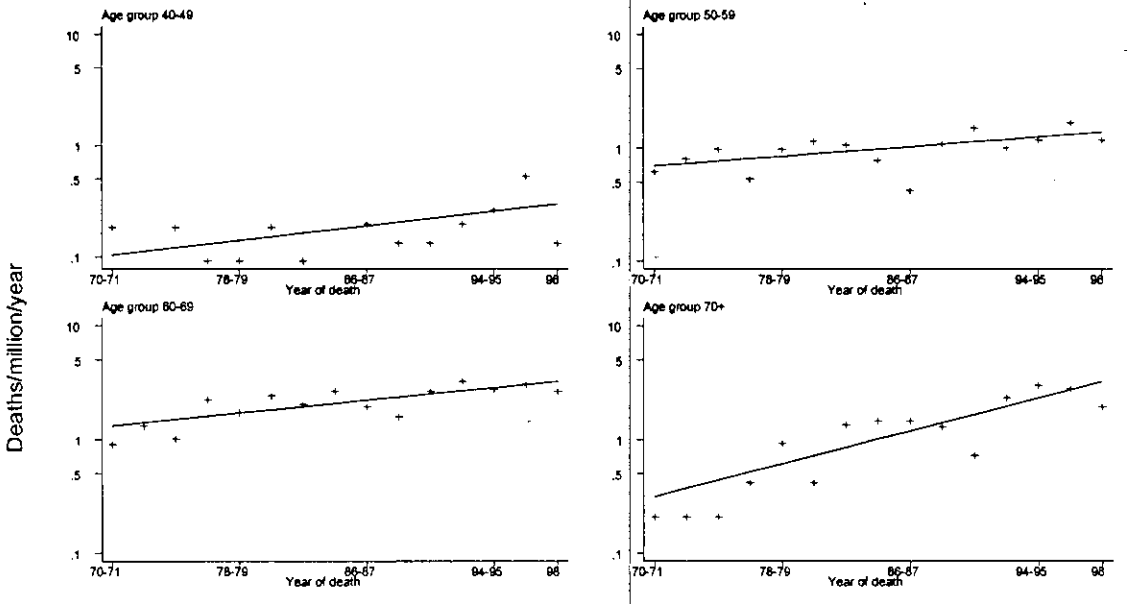
Figure 2 shows average annual age- and sex-specific mortality rates over the whole study period 1970-98. The median age at death was 65 years. Below 40 years of age mortality rates were extremely low (< 0.1/million/year). Thereafter they increased, reaching a peak of around 2/million/year in the age group 60-69 years, after which they declined. This decline in the oldest age groups has been noted in other countries and a possible explanation for this phenomenon is poorer case ascertainment in these older age groups, in which other causes of dementia are common.

Figure 2 Age- and sex-specific mortality rates from sporadic CJD in the UK, 1970-1998



An analysis of age specific trends from 1970 to 1998 (Figure 3) shows that the greatest relative increase in mortality occurred in those aged 70 years and above, and that currently the mortality rate in this age group is similar to that in the age group 60-69 years. This observation is consistent with improved case ascertainment in the elderly in recent years. In both the age groups 60-69 and 70+ years the temporal increases in mortality are highly statistically significant ($p < 0.001$). In the younger age groups there is also some evidence of increases in mortality over time (for the age group 50-59 years, $p = 0.01$; for the age group 40-49 years, $p = 0.1$)

Figure 3 Trends in mortality from sporadic CJD by age



Note: Rates are plotted on a logarithmic scale.

Table 2 presents the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged less than 50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 15 per year in the UK in recent years.

Standardised mortality ratios (SMRs) for the 10 standard regions of Great Britain for the period 1st January 1985 to 31st December 1998 are shown in Figure 4. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p = 0.20$). Areas of relatively high mortality are the South West region (SMR=126), Wales (SMR=120) and Scotland (SMR=117). Low mortality rates were observed in the West Midlands (SMR=67), and the East Midlands (SMR=80). The SMRs for the other six regions all lay between 90 and 105. The highest SMR (126 in the South West) arose from 53 cases observed compared with 42 expected, an excess of about 11 cases over a period of 14 years. In Wales and Scotland the excess numbers of cases were approximately 5 and 7 respectively.

Table 2 **Cases of sporadic Creutzfeldt-Jakob Disease in England and Wales (1970-1984) and the U.K. (from 1985)**

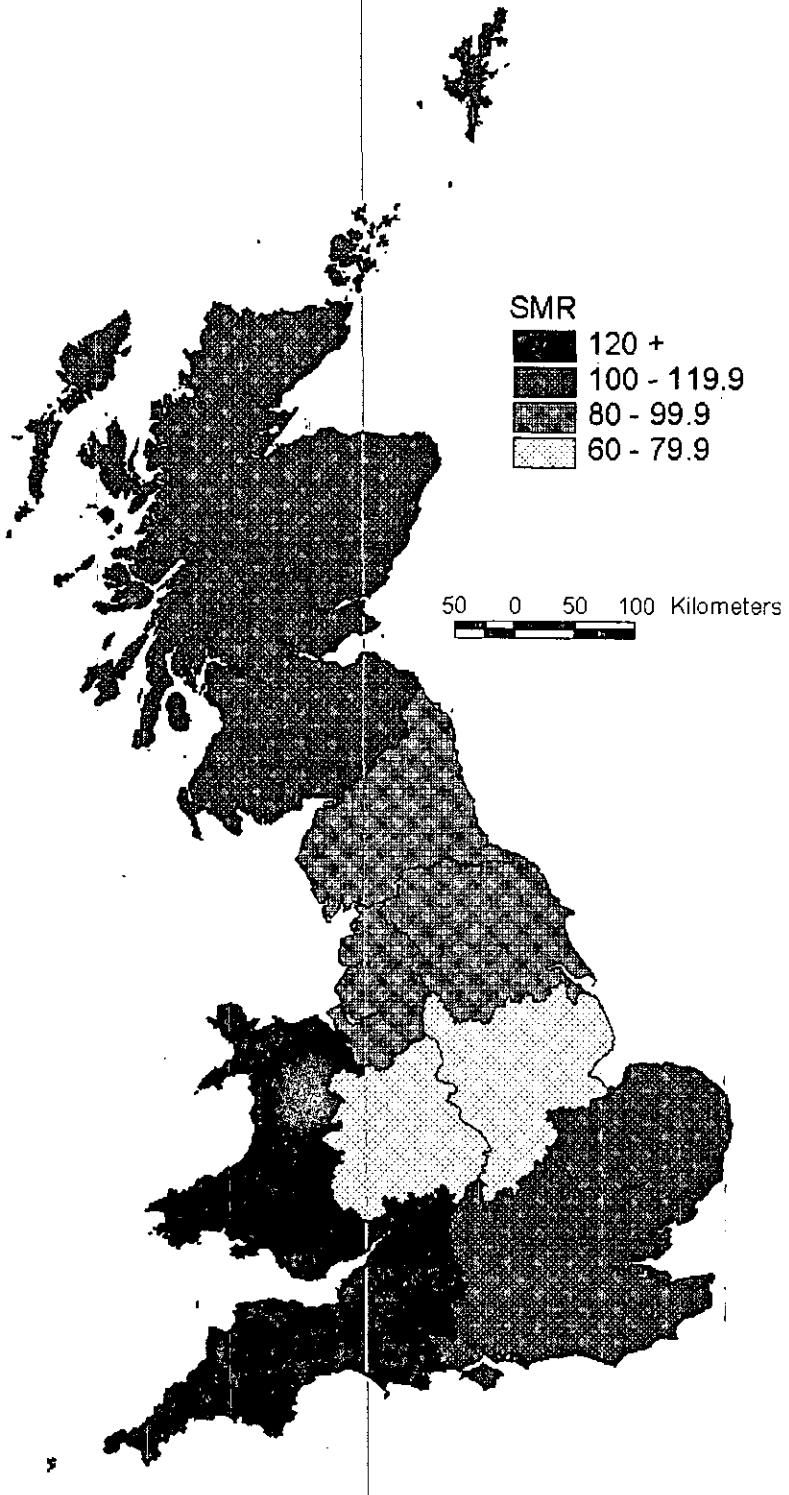
Age at death (years)	Year of death															
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[1]	86-87	88-89	90-91	92-93	94-95	96-97[2]	98	Total[2]
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0 (0)	**1 (0)**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0)	**1 (0)**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1 (0)	**14 (0)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	1 (0)	**32 (0)**
50-59	7	9	11	6	11	13	12	9	5	13	18	12	14	20	7 (0)	**167 (0)**
60-69	9	13	10	22	17	24	20	28	22	18	30	37	31	35	15 (3)	**332 (3)**
70 +	2	2	2	4	9	4	13	16	18	16	9	29	37	35	12 (0)	**208 (0)**
Total	**21**	**24**	**25**	**35**	**40**	**45**	**47**	**57**	**49**	**50**[3]	**60**	**81**	**86**	**99**	**36 (3)**	**755 (3)**

[1] Up to and including 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included

[2] Deaths up to 31st December 1998. Numbers in parentheses indicate additional cases alive on 31st December 1998

[3] Includes one case whose age at death was unknown

Figure 4 **Standardised mortality ratios (SMRS) by standard region, Great Britain, 1985 - December 1998**



2.2 New Variant Creutzfeldt-Jakob disease

Up to 31st December 1998, 35 cases of nvCJD had been identified in the UK (33 definite, 2 probable), all of whom had died. Twenty of the 35 cases were women. The median age at onset of disease was 28 years and the median age at death 29 years (compared with 65 years for the median age at death for sporadic CJD). The youngest case was aged 16 years at onset while the oldest case was aged 52 years. The median duration of illness was 14 months (range 8-38). The median delay between onset of disease and confirmation of the diagnosis of nvCJD was 15 months (with a range 7.2 - 32.0 months). This has not decreased over time. Since the first case of nvCJD, with onset in early 1994, there has been no evidence that the rate of occurrence of new cases has increased over time (Figure 5). Analyses which adjust for delays in reporting and confirmation have found no evidence that the incidence rate of nvCJD has increased during the period 1994-1997 (P.Farringdon, personal communication).

Figure 6 shows the geographical distribution by place of residence at onset, of the 34 cases of nvCJD with onset in Great Britain. This shows that the cases to date have been widely spread geographically.

Figure 5 **Cases of nvCJD by date of onset**

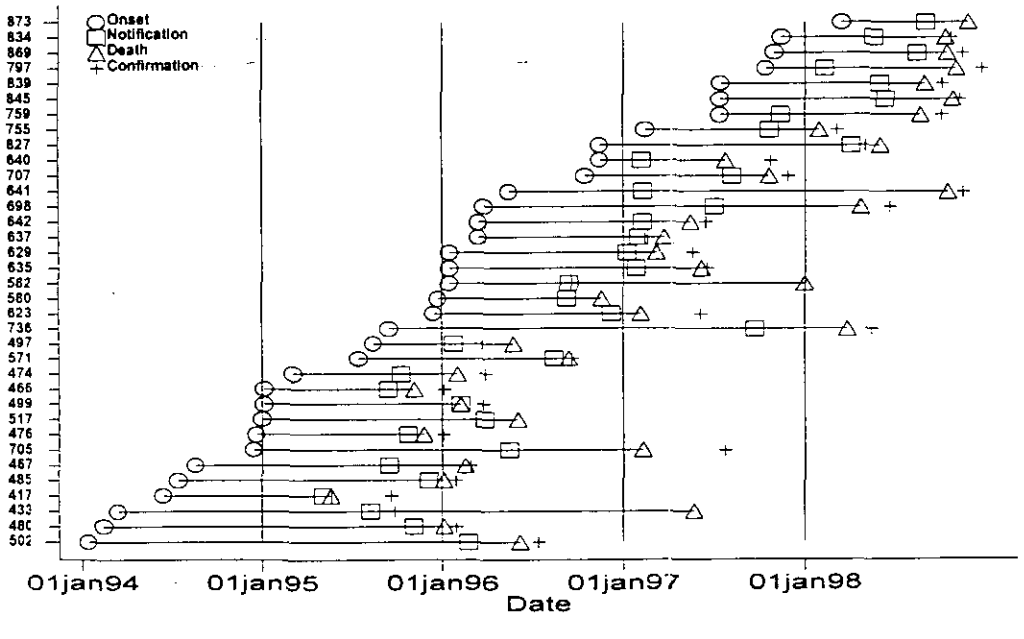


Figure 6 Geographical distribution of places of residence at onset of 34 cases of nvCJD (resident in Great Britain at the date of onset of symptoms)

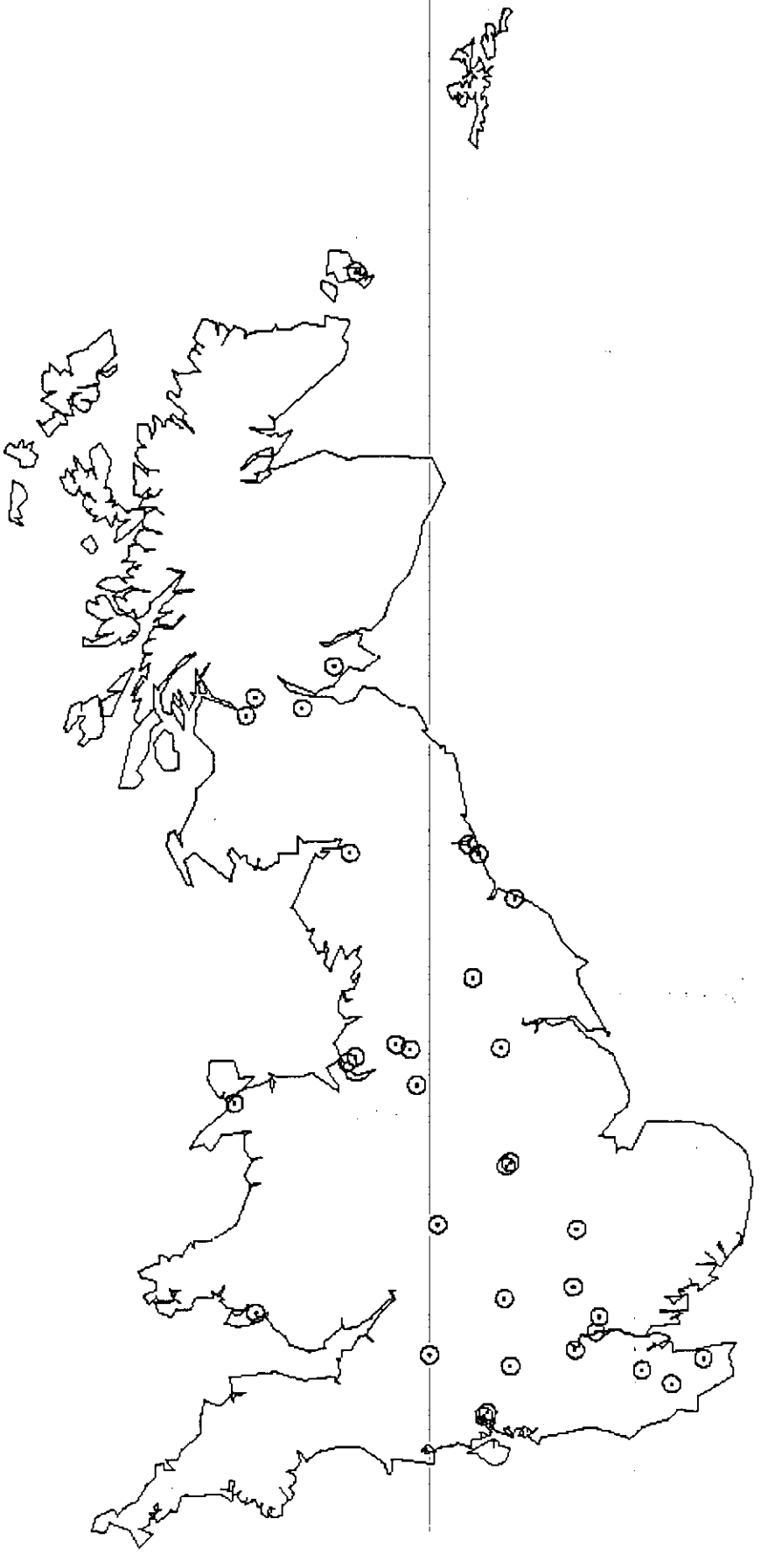


Table 3 shows the months of the year in which onset and death occurred for the 35 nvCJD cases. There appears to be an excess of cases with onset of the disease during the period November to March.

Table 3 Month of onset and death of 35 cases of nvCJD

Month	Number of onsets	Number of deaths
January	7	3
February	2	5
March	6	3
April	0	1
May	1	5
June	1	3
July	5	1
August	2	2
September	1	1
October	2	6
November	4	4
December	4	1
Total	35	35

To investigate the statistical significance of this observation we performed some simulations. In each simulation the 35 cases were randomly allocated to a month of the year (ignoring the variations in length between different months). For each simulation the maximum number of cases falling in a single month and in blocks of 2, 3, 4, 5 and 6 consecutive months was recorded. The proportion of simulated values equal to or exceeding the observed maximum numbers of onsets and deaths occurring in each block size was then evaluated over 10,000 simulations. These results are shown in Table 4.

Table 4 Maximum observed incidence of onset and death for 35 cases of nvCJD over 1,2,3,4,5, and 6 month blocks with corresponding probabilities derived by simulation

Size of block (months)	Observed maximum of onsets	Proportion of simulations in which this value equalled or exceeded	Observed maximum of deaths	Proportion of simulations in which this value equalled or exceeded
1	7	0.27	6	0.65
2	11	0.24	10	0.49
3	15	0.16	11	0.98
4	19	0.09	14	0.98
5	23	0.04	19	0.56
6	25	0.08	22	0.54

There was no evidence of a seasonal pattern of deaths. There is weak evidence of seasonality in dates of onset. Twenty four of the 35 cases had onsets from November to March ($p = 0.04$). Cases frequently present initially with psychiatric symptoms including depression. It is possible that seasonal climatic changes or increased stress levels over the Christmas period may precipitate behavioural changes which are identified as the onset of illness, or that the behavioural changes have already begun and are first noticed around Christmas when families may spend more time together. Given the likely long incubation period of the disease it seems unlikely the seasonal pattern observed in onsets results from any seasonality in exposure to the infectious agent.

2.3 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 1998, 33 cases of CJD attributable to iatrogenic exposure have been identified, 6 in individuals receiving dura mater implants and 27 in individuals who had received human-derived growth hormone (hGH) or gonadotrophin. The mean age at death of the latter group is 28.7 years (with a range of 20-45 years) and for the dura mater cases is 43.3 years (range 27-59 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Between 1st May 1990 and 31st December 1998 there were 24 CJD deaths in hGH recipients, an average of nearly 3 deaths per year.

2.4 Familial Creutzfeldt-Jakob disease

Thirty-four cases of familial CJD have been identified since 1970, excluding cases of GSS. Of these, 32 were resident in England and 2 were resident in Wales. Thirteen of the cases had insertions in the coding region of the PrP gene, 8 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129), 1 at codon 117 (Ala-Val) and 1 at codon 210 (Val-Ile). Nine were identified as familial on the basis of relatives known to have had CJD (one with a relative known to have an insertion, one with a relative known to have the codon 200 mutation). The mean age at death was 55.8 years (with a range 38 - 68 years).

2.5 An analysis of clustering of CJD in space and time

The method of Knox,[4,5] was used to look for evidence of clustering of cases of CJD in space and time (which might provide evidence of case-to-case transmission or a common source of infection). (Note: P-values were estimated using simulation. In previous reports they were calculated assuming that the number of pairs in an individual cell was distributed as a Poisson random variable.) Cases of sporadic CJD and of new variant CJD were analysed separately.

Sporadic CJD

Four hundred and sixty cases of sporadic CJD identified in Great Britain, with onset on or after 1st January 1985, were included in the analyses. When known, the date of clinical onset was used as the time point in the analyses. When date of onset was unknown (5.1% of cases), it was set at 4 months prior to the date of death (4 months being the median duration from onset to death for cases with known date of onset).

Table 5 **Space-time clustering of dates and places of onset of 460 cases of sporadic Creutzfeldt-Jakob disease in Great Britain, with onset between January 1985 and December 1998: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other**

Time between dates of onset*	Distance between places of residence at onset							
	< 5km		< 10 km		< 20 km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	5	7.3	13	12.6	32	37.6	106	113.0
1-3 months	11	11.3	21	22.4	52	58.7	161	173.7
3-6 months	19	17.0	35	34.5	90	90.0	276	268.2
6-12 months	22	33.2	57	67.3	160	174.9	511	518.1
1-2 years	63	62.3	115	126.1	289	323.7	899	966.8
2-3 years	58	56.7	102	115.3	303	298.5	900	884.1
3-4 years	45	51.5	101	103.6	257	269.4	775	802.5
4-5 years	46	44.7	99	45.1	256	233.7	663	697.7

Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830

[4] Knox G. Detection of low intensity epidemicity: application to cleft lip and palate. *Br J Prev Soc Med* 1963; **17:** 121-7.

[5] Knox G. Epidemiology of childhood leukaemia in Northumberland and Durham. *Br J Prev Soc Med* 1964; **18:** 17-24.

The results of the Knox analyses of these 460 cases are shown in Table 5. For most space-time combinations the observed number of pairs is close to the number expected under the null hypothesis of no space-time clustering and for no space-time combinations was there a significant excess of the observed number of pair over the expected number.

Analysis of 692 cases of sporadic CJD occurring in England and Wales over the past 28 years (since 1970) is presented in Table 6. (Analysis is restricted to England and Wales, as cases in Scotland and NI were recorded only from 1985 onwards). There is no evidence of space-time clustering of cases in these data.

Table 6 **Space-time clustering of dates and places of onset of 692 cases of sporadic Creutzfeldt-Jakob disease in England and Wales, January 1970 to December 1998: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other**

Time* between dates of onset	Distance between places of residence at onset							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	5	7.7	13	18.9	46	52.7	153	166.1
1-3 months	11	11.8	24	28.6	67	79.5	220	250.8
3-6 months	22	17.9	43	44.1	122	121.9	400	388.6
6-12 months	31	35.2	81	87.1	243	238.2	749	760.5
1-2 years	69	66.6	149	166.1	434	457.5	1367	1458.4
2-3 years	67	63.9	145	158.0	442	435.9	1409	1384.6
3-4 years	58	59.7	130	146.9	395	407.1	1270	1296.0
4-5 years	64	55.7	142	136.5	380	377.8	1172	1191.8
5-6 years	59	50.7	140	125.2	362	343.6	1106	1094.1
6-7 years	36	46.3	108	114.0	313	315.8	1011	1000.7
7-8 years	54	44.8	122	109.4	320	304.6	984	962.9
8-9 years	45	40.7	96	98.7	272	276.1	905	876.6
9-10 years	42	42.9	102	104.8	310	290.9	954	929.7
10-15 years	161	178.9	435	441.0	1181	1217.9	3832	3866.6
15-20 years	117	114.4	311	279.6	810	770.0	2603	2463.4

* Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830, 2195, 2560, 2925, 3285, 3655, 5490, 7310

New variant CJD

The geographical distribution of 26 cases of nvCJD, identified in Great Britain up to 31st August 1998, was examined in relation to their proximity to rendering plants during the 1980s. No convincing evidence of clustering in relation to rendering plants was found[6]. Knox analyses similar to those above were performed for the 34 cases of new variant CJD identified in Great Britain up to 31st December 1998. The results of these analyses are presented in Table 7. None of the cells produced an excess of observed over expected cases which is statistically significant at the 5% level.

Table 7 **Space-time clustering of dates and places of onset of 34 cases of new variant Creutzfeldt-Jakob disease in Great Britain, identified up to 31st December 1998: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other**

Time* between dates of onset	Distance between places of residence at onset							
	< 5km		< 10 km		< 20 km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	0	0.1	0	0.3	0	0.4	2	1.7
1-3 months	1	0.2	1	0.3	1	0.4	3	1.7
3-6 months	0	0.3	0	0.5	0	0.7	3	2.9
6-12 months	0	0.5	0	0.9	0	1.3	1	5.6
1-2 years	1	1.1	2	1.8	4	2.6	13	10.3
2-3 years	0	0.5	1	0.8	1	1.1	4	4.6

* Critical times used were (in days): 35, 95, 185, 370, 735, 1100

[6] Cousens S.N. et al. Geographical distribution of variant CJD in the UK (excluding Northern Ireland). *The Lancet* 1999; **353**:18-21.

SECTION 3

3. Case-Control Study

Methods

A case-control study of CJD has been carried out in the UK since May 1990 to investigate potential risk factors for the disease. Relatives of patients with suspect CJD have been interviewed using a standard questionnaire which includes a wide range of questions relating to putative risk factors for CJD including occupational, dietary and medical history. Up until 1997, for each suspect case, a patient at the same hospital, matched for sex and age ± 4 years, was identified as a control. Individuals with diseases which might be confused clinically with CJD were excluded from being controls. When possible, a relative of the same degree as for the case was interviewed using the standard questionnaire. If this was not possible the control was interviewed directly using the standard questionnaire. At the end of 1997 the design of the study was changed . Instead of hospital controls, it was decided to recruit community controls through general medical practices. These controls will be more suitable for the investigation of potential medical risk factors. Ethical clearance for the revised study design has now been received from the Multi-Centre Research Ethics Committee for Scotland.

Since recruitment of hospital controls ceased at the end of 1997, there are few additional data on diet and occupation beyond those presented in last year's report. This year we present, instead, an analysis of potential medical risk factors. It should be recognised, however, that controls chosen from hospital patients may have medical histories which are not representative of the general population. This complicates the interpretation of case-control comparisons for medical risk factors and, in particular, we cannot exclude the possibility that important associations are being obscured by the use of an inappropriate control group for such risk factors. The extent to which

selection bias occurred is difficult to quantify before data are available from a "community" control group.

Sporadic CJD

3.1 Medical risk factors for sporadic CJD

All questionnaires available for probable or definite sporadic cases since May 1990 and their controls were reviewed and data on medical history (transplants, surgery, hospital admissions, courses of injectable therapy, etc) extracted. In addition, data on social contact with cases of dementia, and on acupuncture, tattooing, body and ear piercing were recorded.

Data were available for 216 of 331 cases (65%). For all cases information was obtained from a relative. For 113 matched controls (52%) information was also obtained from a relative while for the remaining 103 matched controls information was obtained directly from the control. Table 8 presents a comparison of cases and controls with respect to their histories of surgery and hospital admissions.

There was no evidence that having undergone an operation was associated with increased risk of sporadic CJD. The numbers of operations undergone by those cases and controls with a history of an operation was similar (cases, mean 2.4, range 1 to 10; controls, mean 2.6, range 1 to 22). Nor was there any evidence that a particular type of operation (abdominal, neurological, orthopaedic, eye) was associated with increased risk of sporadic CJD, with odds ratios in the range 0.6 to 1.3. One control but no cases had ever received an organ transplant. Similar proportions of cases and controls had been admitted to hospital for reasons other than surgery. There was no indication that, among those with a history of such admissions, cases had been admitted more often than controls (cases, mean 1.8, range 1 to 7; controls, mean 2.8, range 1 to 17).

Table 8 **Reported exposure history of 216 cases of sporadic CJD and their age and sex-matched hospital controls with respect to surgical procedures and hospital admissions**

Exposure		Number (%) of cases (N=216)	Number (%) of controls (N=216)	Odds ratio (95% c.i.)	p-value
Any Operation	No	41 (19)	42 (19)	1.0	
	Yes	175 (81)	174 (81)	1.03 (0.63, 1.71)	0.90
Abdominal Operation	No	148 (69)	130 (60)	1.0	
	Yes	68 (31)	86 (40)	0.68 (0.46,1.03)	0.07
Neurological Operations	No	212 (98)	212 (98)	1.0	
	Yes	4 (2)	4 (2)	1.00 (0.25,3.99)	1.00
Orthopaedic Operations	No	180 (83)	186 (86)	1.0	
	Yes	36 (17)	30 (14)	1.21 (0.74, 2.00)	0.58
Eye Operations	No	204 (94)	201 (93)	1.0	
	Yes	12 (6)	15 (7)	0.79 (0.36, 1.73)	0.36
Other Operations	No	76 (35)	92 (43)	1.0	
	Yes	140 (65)	124 (57)	1.40 (0.93, 2.10)	0.11
Other Hospital Admissions	No	77 (36)	76 (35)	1.0	
	Childbirth only	31 (14)	18 (8)	2.04 (0.93, 4.49)	0.07
	Yes	108 (50)	122 (56)	0.92 (0.61, 1.39)	0.71

Table 9 presents the distribution of cases and controls with respect to other medical "exposures" and with respect to non-medical procedures involving breakage of the skin. There was no evidence that cases were more likely to have a history of regular visits to their GP or to a hospital outpatients' department. Only 2 cases and 2 controls had a history of chronic bowel disease while 3 controls but no cases had a history of insulin-dependent diabetes. Cases were less likely than controls to have ever received a blood transfusion. There was no evidence that cases were more likely than controls to have been to see a psychiatrist in the past, to have received medical therapy involving a course of injections, or to have had glandular fever. Slightly more cases than controls were reported to have undergone acupuncture (9% versus 6%) but this difference was not statistically significant ($p = 0.35$). Fewer cases than controls had been tattooed while the prevalence of ear/body piercing was similar in the two groups.

Table 9 **Reported exposure history of 216 cases of sporadic CJD and their age and sex-matched hospital controls with respect to other potential medical risk factors and body piercing**

Exposure		Number (%) of cases (N=216)	Number (%) of controls (N=216)	Odds ratio (95% c.i.)	p-value
Regular GP/OPD	No	114 (53)	101 (47)	1.0	
Attendance	Yes	102 (47)	115 (53)	0.79 (0.54, 1.15)	0.21
Blood	No	199 (92)	180 (83)	1.0	
Transfusion	Yes	17 (8)	36 (17)	0.42 (0.23,0.79)	0.005
Psychiatric	No	186 (86)	189 (88)	1.0	
Consultation	Yes	30 (14)	27 (13)	1.13 (0.65,1.95)	0.67
Course of	No	195 (90)	185 (86)	1.0	
Injections	Yes	21 (10)	31 (14)	0.63 (0.34, 1.16)	0.13
History of	No	209 (97)	211 (98)	1.0	
glandular fever	Yes	7 (3)	5 (2)	1.40 (0.44, 4.41)	0.56
Acupuncture	No	197 (91)	202 (94)	1.0	
	Yes	19 (9)	14 (6)	1.42 (0.68, 2.97)	0.35
Tattooing	No	212 (98)	204 (94)	1.0	
	Yes	4 (2)	12 (6)	0.33 (0.11, 1.03)	0.05
Ear/body	No	140 (64)	145 (67)	1.0	
Piercing	Yes	76 (35)	71 (33)	1.17 (0.71, 1.92)	0.53

More cases than controls (35 versus 16) were reported as having a family history of dementia (not identified as CJD) (odds ratio = 2.58, 95% c.i. 1.33 to 5.03, p = 0.03).

Summary

These largely negative findings with respect to medical history and risk of sporadic CJD must be interpreted with caution for several reasons.

First, the controls used in the comparison were recruited from among inpatients in the same hospitals as the cases. The interviewer tried to exclude from the recorded medical histories any events related to the current hospital admission, but sometimes it was difficult to ensure that this had been achieved. It is also possible that the previous medical history of the hospital controls is not representative of that of the

population as a whole. If hospital controls have, for example, undergone more surgical procedures than the general population then their use in this study may obscure any increased risk of sporadic CJD associated with such procedures. The finding that cases were less likely than controls to have received a blood transfusion perhaps reflects such selection bias.

Second, information on medical history was obtained through interview with a relative and the history obtained may have been incomplete. This is less likely to have been so for the controls (about half of all controls) who were interviewed directly. Restricting the analysis only to those pairs in which information on the control was obtained from a relative did not alter the findings. In this restricted analysis 81% of cases compared with 79% of controls had a history of surgery. The proportion of cases and controls with a history of previous admission to hospital other than for surgery was similar (46% versus 42%). A higher proportion of cases than controls had been admitted only to deliver a child (18% versus 5%, $p = 0.007$). Conversely, fewer cases than controls had been admitted for reasons other than childbirth (28% versus 37%). Blood transfusion remained less common among cases than controls (9% versus 16%) but this difference was no longer statistically significant ($p = 0.11$). More cases than controls had seen a psychiatrist (14% versus 9%) and had a history of ear/body piercing (39% versus 31%) but neither of these differences were statistically significant ($p = 0.22$ and 0.11 respectively).

Third, even if it were possible to demonstrate clearly that none of the factors considered here were important in the transmission of sporadic CJD, it would not be possible to extrapolate those conclusions to nvCJD, whose pathogenesis appears to differ from that of sporadic CJD in a number of important respects and whose agent may be much more prevalent in the population than that of sporadic CJD.

Cases were more likely than controls to have a family history of dementia. We are unsure of how to interpret this finding. One interpretation is that in some cases with a family history of 'dementia', the affected relative had died of CJD but this diagnosis had either not been recognised or was not known to the family. (This might indicate misclassification of some familial cases as sporadic cases). However it is also possible that such an association arose through recall bias, relatives of individuals

with a dementia perhaps being more likely to recall other members of the family with dementia than relatives of a patient without dementia.

As described above, the design of the case-control study has now been revised to address some of the limitations in respect to the examination of medical risk factors. In future the study will recruit community controls through general practices rather than hospital controls. In addition, it is planned to obtain data on medical histories directly from GPs' records as well as through interview.

New Variant CJD

These analyses are based on data from 35 cases of new variant CJD and 25 age- and sex-matched hospital controls.

3.2 Medical risk factors for nvCJD

Two cases had a definite history of blood transfusion. One had received blood following a road traffic accident some 18 years before disease onset, while the second had received an exchange transfusion at birth, 24 years before disease onset. A further case might have received a transfusion during a hysterectomy about 1 year prior to disease onset. Three of the controls had also received blood transfusions. Fourteen of the cases had no history of any operation/surgical procedure (other than dental procedures) compared with 5 of the controls. A list of surgical procedures undergone by cases and controls is presented in Table 10.

There is no evidence to suggest that cases were more likely than controls to have had operations in the past. This finding should be interpreted with some caution, however, because of the potential bias associated with the use of a control group chosen from hospital patients (as discussed in previous section).

Table 10 **List of operations undergone by 35 cases of new variant CJD and 25 hospital controls**

Cases	Controls
Tonsillectomy (x 4)	Tonsillectomy (x 4)
Appendectomy (x 2)	Appendectomy (x 4)
Caesarean section (x 4)	Caesarean section
Orthopaedic (x 5)	Orthopaedic (x 2)
Hysterectomy (x 2)	Sterilisation
Ectopic pregnancy	Vasectomy (x 2)
Hernia	Gall bladder operation
Mastoidectomy	Removal of adenoids
Hydrocele	Removal of lump/nodule (x 2)
Sutures to wound (x 9)	Sutures to wound (x 7)
D + C	Laparoscopy
Colonoscopy	Squint correction (x 2)
Laparoscopy (x2)	Arthroscopy
Gastric lavage	Arteriosis
Sinusotomy	Nose repair
Eye surgery	Bladder incision
	Ear surgery
	Bone removal after head injury

3.3 Dietary risk factors for nvCJD

The reported consumption of various different meats by cases and controls after 1985 is shown in Table 11. One case was excluded from the analysis because consumption of meat and meat products after 1985 was unknown.

Table 11 **Results of a comparison between 34 cases of new variant Creutzfeldt-Jakob disease and 25 controls with regard to consumption of different types of meat after 1985**

	Post 1985	
	% of cases (n=34)	% of controls (n=25)
Lamb	91	88
Pork	94	92
Beef	97	96
Venison	24	24
Veal	18	28
Poultry	97	96

Almost all cases and controls had eaten lamb, pork, beef or poultry since 1985. Eight cases and 6 controls were reported to have eaten venison since 1985, while 6 cases and 7 controls had eaten veal. Of the 32 cases and 24 controls who had eaten beef

since 1985, cases were reported to consumed beef more frequently than the controls (test for trend: p = 0.02) (Table 12). This finding may be due to recall bias, as we have discussed in previous reports in relation to the results from the case-control study of sporadic CJD. There was no evidence that cases consumed lamb, pork, venison or poultry more frequently than controls (p > 0.10).

Table 12 **Frequency of consumption, since 1985, of beef by 32 cases of nvCJD and 24 controls**

Type of meat	Frequency of consumption	% of cases (n=32)	% of controls (n=24)
Beef	< 1/month	9	38
	1/month or more	19	29
	1/week or more	72	33

Most cases and controls had eaten sausages, liver, puddings, burgers and meat pies since 1985 (Table 13). About one-third to a half of cases and controls were reported to have eaten kidneys, haggis and faggots (Table 13). No cases or controls were reported to have ever eaten eyes after 1985, while only one control was reported to have tried "a spoonful" of brains on one occasion, in Italy in the mid 1980s. Only one case (post 1985) and one control (prior to 1985) were recorded as having eaten sweetbreads. There were no striking differences between the proportions of cases and controls eating any of these items.

Table 13 **Results of a comparison between 34 cases of nvCJD and 25 controls with regard to consumption of various animal "products"**

	Post 1985	
	% of cases (n=34)	% of controls (n=25)
Sausages	94	96
Liver	59	84
Kidney	32	42
Puddings	59	48
Haggis	26	28
Burgers	94	83
Meat pies	92	83
Faggots	39	29

One route through which bovine brain and spinal cord may have entered the human food supply is through mechanically recovered meat (MRM). Data on the frequency of consumption of three of the food items listed above which might contain MRM (sausages, burgers, meat pies) were combined to provide an estimate of the frequency with which cases might have been exposed to MRM in the period since 1985 (Table 14). Where the frequency of consumption of one or more of these food items was unknown the modal consumption of that food item amongst the other cases (or controls for the control group) was taken.

Table 14 **Comparison of nvCJD cases and controls with respect to the frequency of consumption, since 1985 of foodstuffs which might contain mechanically recovered meat (sausages, burgers, meat pies)**

Frequency of consumption of sausages, burgers or meat pies	% of cases (n=34)	% of controls (n=24)
< 1 per month	3	4
several times per month	18	13
more than once per week	79	83

This analysis indicates very high rates of consumption of these food items among both cases and controls, without indicating major differences between cases and controls. The data suggest that, among the population in the age range considered (mid-teens to forties), exposure to MRM is likely to have been very widespread and have occurred on many occasions.

3.4 Occupation and new variant CJD

Table 15 presents a list of occupations for cases and controls. No occupation stands out as unusually common among the cases.

Table 15 **List of lifetime occupations for 35 cases of new variant Creutzfeldt-Jakob disease and 25 controls**

Cases	Controls
Clerical worker (x 9)	Clerical worker (x 6)
Catering worker (x 9)	Catering worker (x 5)
Shop assistant/retail (x 8)	Shop assistant/retail (x 5)
Factory worker (x 5)	Factory worker (x 4)
Engineering (x 3)	Engineering (x 3)
Nurse (x 3)	Hairdresser (x 2)
Bar worker (x 3)	Dental nurse
Cleaner/domestic (x 2)	Cleaner/domestic
Computing (x 2)	Chicken factory worker
Horticulture (x 2)	Management
Cable layer (x 2)	Bar worker
Kennels (x2)	Miner
Driver (x2)	Fireman
Hairdresser	Fairground worker
Stable hand	Performer
Solicitor	Road layer
Debt collector	Labourer
Laundrette worker	Bottling
Forestry worker	Driver/porter
RAF Policeman	Painter/decorator
Energy Industry	Sewing Machinist
Paper round	Care Attendant
Coastguard	Toolmaker
Plumber	Printing
Milkman	Roofer
Dental assistant	Technical Writer
Receptionist	Translator
Painting models	Interviewer
Pet shop	French Polisher
Dustman	Animal Farmer
Naval radio operator	
Labourer	
Butcher	
Metal Cutter	
Paper Recycling	
Draught Exclusion	

Both cases and controls had experience of a wide range of occupations, without any occupation being particularly common among cases. There is no obvious evidence of an occupational risk for nvCJD.

Summary

We have found no evidence of any iatrogenic or occupational risk for nvCJD. Although the majority of cases had undergone operations, their history in that respect was similar to that of controls. Cases were reported to eat beef more frequently than controls. However, this finding is extremely difficult to interpret because of the problem of recall bias, previously discussed in the context of sporadic CJD. Perhaps the most striking finding is the degree of exposure of the population to food items that might contain MRM.

SECTION 4

Neuropathology

4.1 Statement of Progress

The Neuropathology Laboratory in the CJD Unit continues to sustain an increasing workload in terms of both diagnostic and research activities. One major development in 1998 was the establishment of a protein laboratory, which has allowed an expansion of the laboratory activities to include biochemical techniques eg Western blotting. This, in combination with clinical, neuropathological and genetic data will allow more precise characterisation of all CJD cases. The laboratory has continued to maintain close liaison with other neuropathology laboratories across the UK in order to provide support for autopsy activities, to make arrangements for the collection and transport of diagnostic material and to facilitate brain banking activities. The high post mortem and referral rates for suspected CJD cases have been maintained in 1998. We are most grateful to all the neuropathologists, general pathologists and their technical staff in the UK for their continuing support of the CJD Surveillance Project.

4.2 Surveillance and Workload during 1997/98

A detailed breakdown of the laboratory activities is summarised in Tables 16 and 17. These demonstrate the increased workload within the laboratory for diagnostic specimens, which has been maintained from previous years as a consequence of the identification of the new variant form of CJD. Overseas referrals continue to be an important part of the workload, but the core diagnostic activities relate to the identification of CJD cases in the UK. As in previous years, a number of cases referred to the laboratory were diagnosed with other neurological disorders, the commonest of which were Alzheimer's disease and dementia with Lewy bodies. The laboratory uses internationally agreed diagnostic criteria for these two disorders, along

with similar guidelines for the investigation and diagnosis of rarer neurological disorders where appropriate. In addition to these cases, neuropathological diagnostic opinion is requested on referral material from the UK and overseas in the form of prepared histological sections which do not require additional technical work in the laboratory.

Table 16 Breakdown of Laboratory Activities: Period 1st May 1997 – 31st December 1998

	CURRENT YEAR (20 months)	***PREVIOUS YEAR*** (12 months)
SUSPECTED CASES (UK)		
No evidence of CJD	46	*26*
Iatrogenic CJD (GHT)	7	*6*
Gerstmann-Straussler-Scheinker syndrome	3	*0*
Fatal Familial Insomnia	0	*0*
Classical CJD	64	*29*
nvCJD	17	*7*
Other †	19	*7*
Alzheimer's disease	15	*15*
Organic dementias	8	*6*
SUSPECTED CASES (European Union)	17	*25*
SUSPECTED CASES (Rest of World)	22	*27*
Sub Total (a)	**218**	***148***
OTHER REFERRALS AND STUDIES§		
Human Studies	75	*23*
Animal Studies	127	*4*
Kuru	14	*7*
Historical CJD cases	3	*2*
Sub total (b)	**219**	***36***
TOTAL NUMBER OF CASES (a+b)	**437**	***184***

NOTES

†Other:

Ischaemia	2	Metabolic disorder	2
Amyloid angiopathy	2	Corticobasal degeneration	1
Hypoxia	4	Oedema, arteriosclerosis, haemorrhage	3
Normal control, age related change	1	Infarction	2
Subcortical gliosis	1	Herpes simplex encephalitis	1

§ Studies:

Human
Study of PrP^C expression in human brain – Dr Jeanne E Bell
Haemophilia – Dr Nigel Cairns, Dr J McLaughlin, Professor M Esiri
Kuru - Dr Catriona McLean, Professor CL Masters

Animal
CJD mouse transmission studies – Dr J W Ironside, Dr Moira Bruce, Professor J Collinge
Feline studies – Dr Alun Williams
Marmoset studies – Dr R Ridley and Dr R Baker

Table 17 **Monthly breakdown of the number of paraffin blocks cut and stained in the CJD laboratory for diagnostic and research purposes (including CNS and other human tissues and non-human research specimens)**

May 1997 - April 1998

	Blocks	Slides
May 1997	194	1729
June 1997	350	2320
July 1997	46	311
August 1997	238	799
September 1997	221	1739
October 1997	275	1012
November 1997	248	1126
December 1997	145	838
January 1998	275	979
February 1998	106	902
March 1998	296	2392
April 1998	318	1434
TOTAL	2712	15581

Monthly Average Block Total: 226
Monthly Average Slide Total: 1298

May 1998 - December 1998

	Blocks	Slides
May 1998	289	1192
June 1998	252	1167
July 1998	209	1163
August 1998	130	883
September 1998	422	1375
October 1998	268	1276
November 1998	129	564
December 1998	128	574
TOTAL	1827	8194

Monthly Average Block Total: 228
Monthly Average Slide Total: 1024

4.3 Protein Laboratory

In 1998, Dr Mark Head joined the CJD Surveillance Unit from a post in New York to establish a laboratory which is dedicated for the study of prion protein by Western blotting and related biochemical techniques. This methodology enhances the diagnostic technology available within the Unit, and will also facilitate identification and sub-classification of CJD cases. The laboratory will also facilitate research in CJD both within the Unit and in collaboration with other centres in the UK and overseas.

4.4 New variant CJD (nvCJD)

Continued research into the neuropathology of nvCJD has employed a range of investigative techniques, resulting in increasing numbers of scientific publications on the detailed cellular neuropathology and diagnostic criteria for nvCJD. Important advances in the pathology of nvCJD have included studies to identify disease-associated prion protein outside the central nervous system in lymphoid tissues, including tonsil, spleen, lymph nodes and gut-associated lymphoid tissue. Much of this research is being performed in collaboration with Professor John Collinge, London and in collaboration with Dr David Hilton, Plymouth. It was possible to identify prion protein by immunocytochemistry in an appendix which was surgically removed from a patient who went on to develop the early symptoms of nvCJD 8 months following this procedure. The Unit is now involved in the planning of a retrospective review of tonsil and appendicectomy specimens using PrP immunocytochemical techniques developed and validated in the Unit for an early start in 1999.

4.5 Brain Banking Activities

The bank of frozen and fixed tissues from the tissue bank was used extensively in 1997/98 for research purposes both within the Unit and with collaborators in the UK and overseas (see Table 18). This has been of particular importance in the

biochemical characterisation of prion protein subtypes in CJD, continuing transmission studies, and as substrates for the development of new biochemical techniques for PrP detection using novel reagents.

The overall activities of the brain and tissue bank continue to increase and additional freezer space has been required in order to accommodate this activity.

4.6 Health and Safety

The laboratory continues to receive numerous requests for advice and guidance on the safe handling of CJD tissues including brain biopsy material, blood and CSF samples, autopsy brain tissues and other organs. General advice on autopsy procedures is also provided (along with appropriate protocols) and information on burial and cremation has also been supplied on several occasions. The publication of the ACDP/SEAC Joint Working Group on these topics has proven to be a successful focus for this aspect of the Unit's activities. The careful attention to health and safety within the Unit has been maintained with no accidents being reported this year and no problems with the handling and transport of materials to and from the laboratory.

4.7 Laboratory Visitors

The laboratory has been visited by neuropathologists, technical staff, students and scientists during 1997/98 for varying periods (Table 19). Several of the students have undertaken research projects in their time within the laboratory, several of which have resulted in scientific publications. The laboratory now accommodates the work of a full-time PhD student in relation to the activities of the protein laboratory under the supervision of Dr Head and Dr Ironside.

Table 18 **National and International Requests for Fixed and Frozen Material from the CJD Surveillance Unit's Brain and Tissue Bank**

May 1997 - April 1998

Recipient	No. of Cases	Recipient	No. of Cases
Dr P Brown, Bethesda, USA	3	Professor N Kopp	5
Dr M Bruce, Edinburgh, UK	1	Professor H Kretzshmar	5
Professor H Budka, Vienna, Austria	1	Professor P Lantos, London, UK	15
Dr A Chakrabarty, Leeds, UK	1	Dr R Lathe, Edinburgh, UK	4
Professor J Collinge, London, UK	22	Dr B Little, Philadelphia, USA	1
Dr D Crooks, Liverpool, UK	2	Professor J Lowe, Nottingham, UK	3
Dr F C Dohan, Memphis, USA	1	Dr D Mann, Manchester, UK	19
Professor M Esiri, Oxford, UK	2	Dr J Morris, Oxford, UK	1
Dr GH George, Saskatoon, Canada	1	Dr J Manson, Edinburgh, UK	5
Professor F Gray, Paris, France	4	Mr G Oniscenko, Russian Federation	2
Dr C Harker Rhodes, Dartmouth, UK	1	Professor M Pires, Porto, Portugal	1
Dr D Hilton, Plymouth, UK	1		

May 1998 - December 1998

Recipient	No. of Cases	Recipient	No. of Cases
Dr P Brown, Bethesda, USA	2	Professor F Gray, Paris, France	2
Dr M Bruce, Edinburgh, UK	21	Dr GH Jansen, Utrecht, Holland	1
Professor J Collinge, London, UK	2	Dr P Scheltens, Amsterdam, Holland	1
Dr P Gambetti, Ohio, USA	7	Dr F Tagliavini, Milan, Italy	2
Dr B Ghetti, Indiana, USA	8	Dr KM Weidenham, New York, USA	1
Dr I Gonzalo, Madrid, Spain	2	Dr JH Xuereb, Cambridge, UK	1

Table 19 **Visitors for training to the CJD Surveillance Unit Neuropathology Laboratory 1997-1998**

Technical Staff

Ms D Brown, NPU, Edinburgh, UK
Ms J Carter, Oxford, UK
Mr W Cooley, Weybridge, UK
Mr D Fettes, Edinburgh, UK
Ms C Firmo, Lisbon, Portugal
Ms A Long, Weybridge, UK
Mr S Mitchell, Cambridge, UK
Ms C Murdoch, Edinburgh, UK
Mr D Redwood, Weybridge, UK

Students

Mr H Hepburn – Scott, Reading, UK
Mr N Holdstock, Edinburgh, UK
Mr M Spencer, Cambridge, UK
Mr Lim Zi Yi, Edinburgh, UK

4.8 Research Projects

The laboratory has undertaken an increasing number of research programmes some funded by external sources (BBSRC and MRC), by the Department of Health and the European Union. The laboratory also contributes to the EC Biomed2 Neuropathology Project headed by Professor Budka and the Biomed2 project for surveillance of CJD in the European Community (led by Professor Will). The BBSRC-funded project has proven invaluable in providing quantitative data on the pathological changes occurring in CJD with particular emphasis in nvCJD. This research will be incorporated into pathological diagnostic criteria for nvCJD and this activity is being expanded by an EC collaborative project which involves quantitation of all aspects of neuropathology and neuroimaging in CJD.

SECTION 5

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SECTION

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Staff based at CJD Surveillance Unit
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Professor RG Will	Director, National CJD Surveillance Unit
Dr JW Ironside	Reader in Pathology
Dr RSG Knight	Consultant Neurologist
Dr JE Bell	Consultant Neuropathologist
Dr G Stewart and Dr M Macleod	Research Registrars
Mrs B Bathgate-Smith	Nurse Practitioner
Mrs K Estibeiro	Molecular biologist
Ms J Mackenzie	Study Co-Ordinator
Mr A Hunter	Business Manager
Mr N Attwood	Database Manager
Mrs L McCardle	Chief MLSO
Mrs M Le Grice, Ms S Lowrie and Ms M Moore	Senior MLSOs
Dr M Head	Research Scientist (molecular and cell biology)
Ms BA Mackenzie	Neuropathology Database Manager/Secretariat
Ms A Honeyman, Miss C Smith	Secretariat

Staff funded by Other Sources

Dr W. Nailon (BBSRC)	Research Scientist (image analysis)
Dr N McLennan (MRC)	Research Scientist (molecular and cell biology)
Mr T Bunn	PhD student
Ms T Lindsay (BIOMED2)	European Study Co-Ordinator
Mrs C Donaldson (BIOMED2)	Secretariat

Epidemiological and Statistical Support
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Professor P Smith	Epidemiologist and Head of Dept of Infectious and Tropical Diseases
Mr S Cousens	Statistician
Ms L Linsell	Statistician