Ninth Annual Report 2000

Creutzfeldt-Jakob Disease Surveillance in the UK

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Summary

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) became a WHO Collaborative Centre for Reference and Research on the Surveillance and Epidemiology of Human Transmissible Spongiform Encephalopathies (TSEs). The information provided in this ninth report continues to provide evidence of a high level of case ascertainment. 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 1990-2000. 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, they reflect changes in incidence.

In 1990-2000 mortality rates from sporadic CJD in England, Scotland, Wales and Northern Ireland were, respectively, 0.75, 0.86, 1.00 and 0.46/million/year. The difference between the rates in each country is not statistically significant (p=0.3). These rates are comparable to those observed in other countries in Europe and elsewhere in the world, including countries which are free of BSE. There was some variation in the observed mortality rates between the different regions within the UK but this variation is not statistically significant (p=0.5). The highest and lowest mortality rates from sporadic CJD were observed in the East Anglia (SMR=129) and East Midlands regions of England (SMR=81). Previous analyses have found no convincing evidence of space-time clustering, and this remains the case for the analyses in this report.

Up until 31 December 2000, there have been 84 deaths from definite or probable variant CJD (vCJD) in the UK (in addition 2 probable cases died in January 2001 and a further 7 probable cases remained alive as at 31 January 2001). Of the 84 deaths to 31 December 2000, 75 were confirmed neuropathologically with a further two awaiting neuropathological confirmation. The clinical, neuropathological and epidemiological features of all these cases of vCJD are remarkably uniform and consistent with previous descriptions. However, a case of neuropathologically confirmed vCJD in an individual who died aged 74 years in October 1999 significantly extends the age range in vCJD.

Analysis of the incidence of vCJD by standard region suggests that the incidence of vCJD in the "North" of Great Britain may be higher than in the "South". The rate ratio (north *vs* south) based on place of residence in 1991 was 1.81 (95% CI 1.20, 2.74). The mean Carstairs' deprivation score for areas of residence of people with vCJD was -0.41 (95% CI -1.02, 0.19), which is close to the national average of zero. Regional rates of vCJD were correlated with consumption of other meat or meat products as classified and recorded by the Household Food Consumption and Expenditure Survey (r =0.73), but not with similar data from the Dietary and Nutritional Survey of British Adults. Five people with vCJD in Leicestershire formed a cluster (p=0.004).

Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - 87 cases of vCJD with available genetic analysis have all been methionine homozygotes. The analyses in this report do not provide conclusive evidence of an increased risk of vCJD associated with past surgery, previous blood transfusion, occupation or a range of dietary factors. However, the power of the case-control study, from which these results are derived, is limited by the relatively small number of cases and controls. For some putative risk factors, such as blood transfusion or surgery, it may be many years before an accurate assessment of risk can be made because of the likely prolonged incubation periods.

SECTION

2

2. Clinical Surveillance

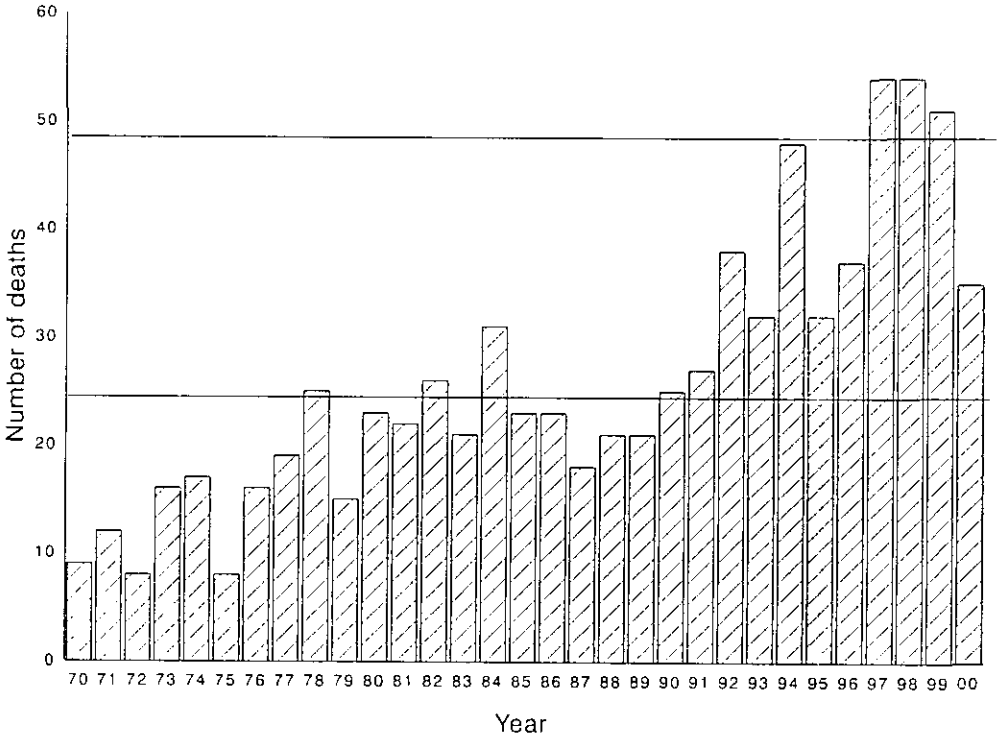
The national surveillance of CJD was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to the emergence of bovine spongiform encephalopathy (BSE). Such a change was recognised in 1996 when vCJD was first described. The NCJDSU 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 NCJDSU (UK) in relation to cases of sporadic, familial, iatrogenic and vCJD diagnosed up to 31st December 2000 (with data ascertained up to 31st January 2001).

2.1 Sporadic Creutzfeldt-Jakob disease

Between 1st January 1970 and 31st December 2000, 888 cases of sporadic CJD were identified in the UK, of which 7 cases were still alive on 31st December. One case was identified in Jersey, which was not included in the following UK analyses. Of these cases, 689 (78%) 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 2000, Figure 1b shows similar data for Scotland and Northern Ireland between 1985 and 2000 and Figure 1c shows the combined number of deaths (i.e. UK) from 1985 to 2000. 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 40 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are

available for Scotland and Northern Ireland there is no clear secular trend although the highest numbers of cases are seen in the two most recent years for which data are complete. Over the period 1990-2000 the average annual mortality rates from sporadic CJD per million population were 0.75 in England, 1.00 in Wales, 0.86 in Scotland and 0.46 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 ($p > 0.2$) (unchanged).

Figure 1a Deaths from sporadic CJD, England and Wales, 1970-2000



Note:
1. The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year
2. Data for 2000 are not yet complete.

Figure 1b Deaths from sporadic CJD, Scotland and Northern Ireland, 1985-2000 (please note different scale from Figure 1a)

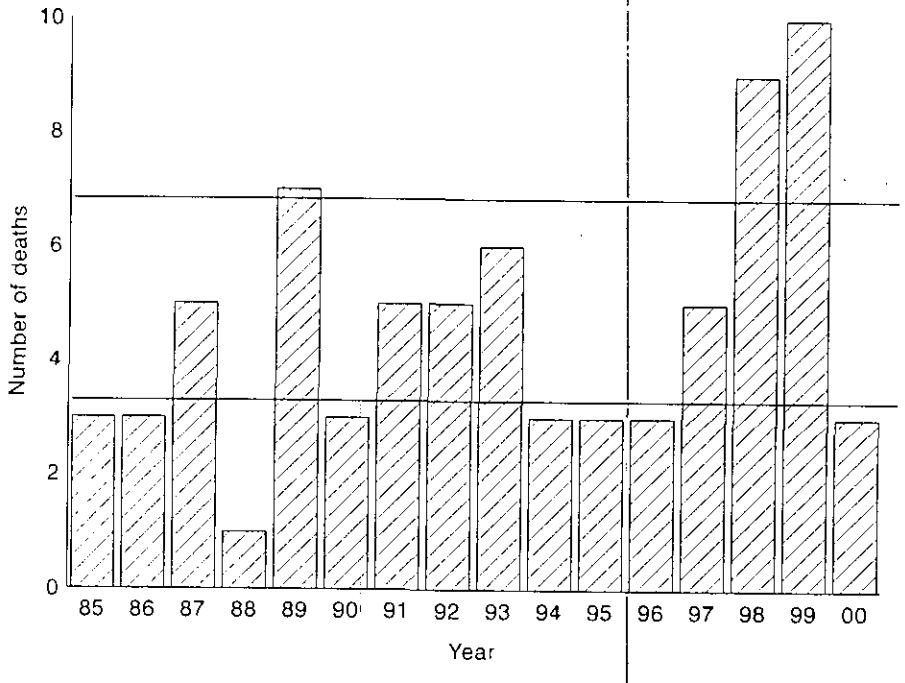
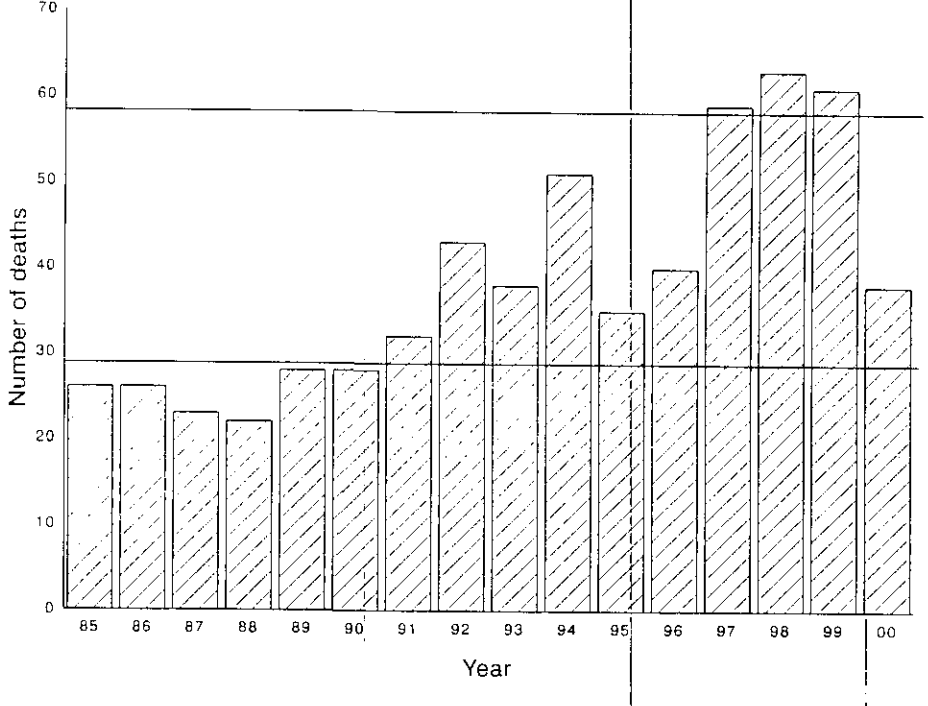


Figure 1c Deaths from sporadic CJD, UK, 1985-2000



Note:
1. The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year
2. Data for 2000 are not yet complete.

Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 01/05/1990 – 31/12/2000

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	1	
Cumbria	8	
Durham	4	28 (0.85)
Northumberland	3	
Tyne & Wear	12	
East Midlands		
Derbyshire	3	
Leicestershire	9	
Lincolnshire	6	27 (0.62)
Northamptonshire	1	
Nottinghamshire	8	
South East		
Bedfordshire	5	
Berkshire	7	
Buckinghamshire	2	
East Sussex	6	
Essex	17	
Greater London	51	133(0.70)
Hampshire	11	
Hertfordshire	4	
Isle of Wight	1	
Kent	9	
Oxfordshire	6	
Surrey	5	
West Sussex	9	
North West		
Cheshire	8	
Greater Manchester	19	55 (0.80)
Lancashire	11	
Merseyside	17	
WALES		
Clwyd	3	
Dyfed	2	
Gwent	4	
Gwynedd	6	
Mid Glamorgan	8	
Powys	2	
South Glamorgan	2	
West Glamorgan	4	
TOTAL FOR WALES		**31 (1.00)**
NORTHERN IRELAND	8	**8 (0.46)**

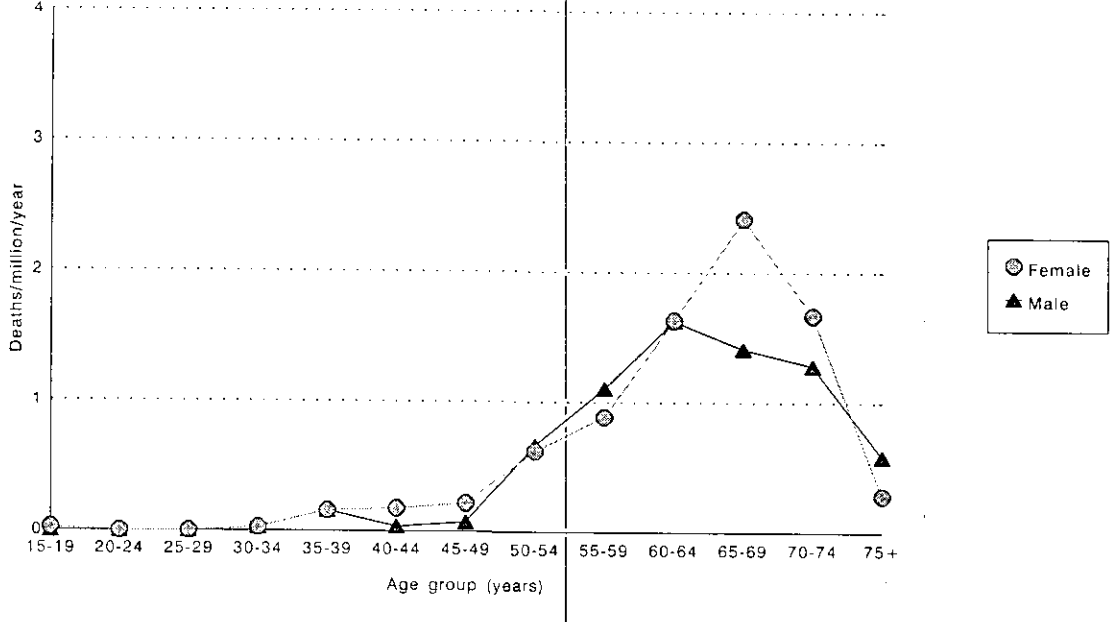
	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
Yorkshire & Humberside		
Humberside	4	
NorthYorkshire	9	
South Yorkshire	11	37 (0.69)
West Yorkshire	13	
East Anglia		
Cambridgeshire	3	
Norfolk	9	23 (1.02)
Suffolk	11	
South West		
Avon	10	
Cornwall	5	
Devon	10	
Dorset	11	53 (1.04)
Gloucestershire	5	
Somerset	5	
Wiltshire	7	
West Midlands		
Hereford & Worcs.	3	
Shropshire	3	
Staffordshire	6	35 (0.62)
Warwickshire	1	
West Mids (Met)	22	
TOTAL FOR ENGLAND		**391 (0.75)**
SCOTLAND		
Borders	1	
Central	5	
Dumfries & Galloway	0	
Fife	2	
Grampian	7	
Highland	1	
Lothian	12	
Strathclyde	16	
Tayside	1	
Islands (Shetland)	2	
Islands (Orkney)	0	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**47 (0.86)**

* Based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 10.67 year period of the study.

Figure 2a, 2b and 2c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-94 and 1995-00, respectively. The median ages of cases at death during these time periods were 64, 66 and 65 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.16/million/year). Thereafter, in all three periods, the mortality rates increased to a peak in 65-74 year olds and then declined. The height of the peak appears to have increased over time (1.96 and 3.28 cases/million/year among 65-69 year olds during 1970-89 and 1990-94, respectively, and 3.32 cases/million/year among 70-74 year olds during 1995-00). The decline in the older age groups has become less dramatic over time with the rate in those over 75 years of age declining to 2.83 cases/million/year in 1995-00, which compares with 2.13 cases/million/year in 1990-94 and 0.38 cases/million/year in 1970-89. These observed differences in the rates in the older age groups over the three time periods could be explained by an increase in case ascertainment over time or a cohort effect.

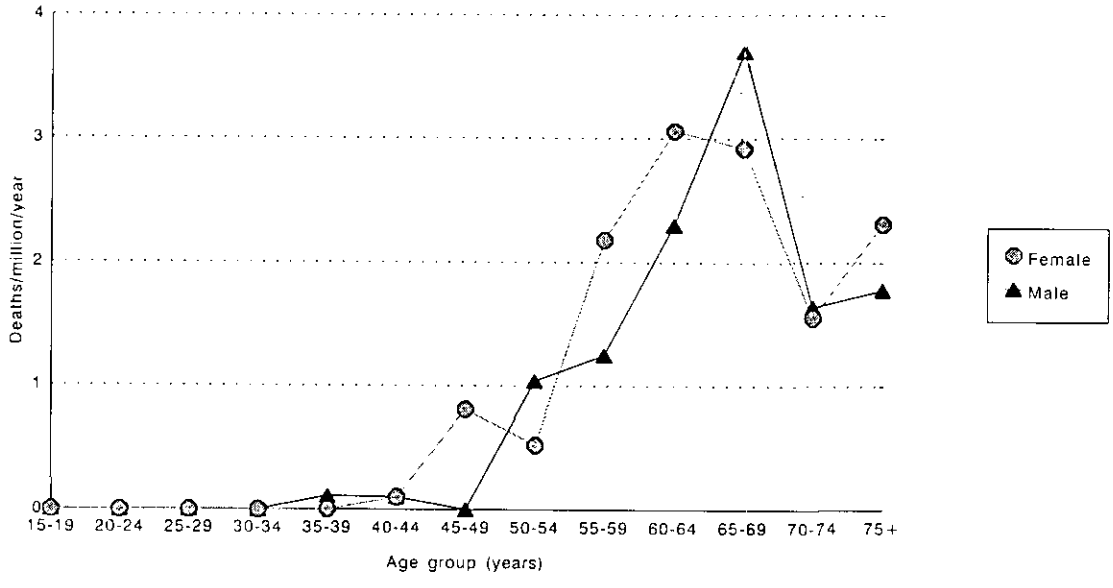
Figure 2a Age- and sex-specific mortality rates from sporadic CJD in the UK: 1970-1989

(NB: from 1970-1985 only England & Wales, thereafter UK)



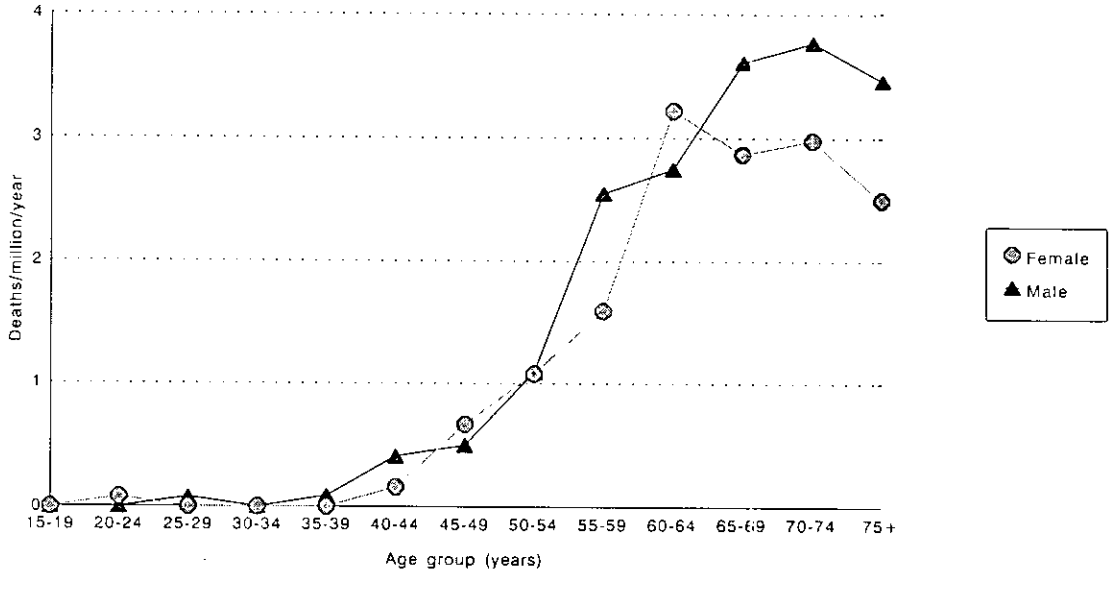
Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

Figure 2b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1994



Mortality rates calculcated using 1991 Census

Figure 2c Age- and sex-specific mortality rates from sporadic CJD in the UK 1995-2000



Mortality rates calculcated using 1991 Census

An analysis of age specific trends from 1970 to 2000 (Figure 3) shows there has been an increase in mortality over time in all age groups, but that the greatest relative increase in mortality has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant ($p < 0.001$ in the age groups 50-59, 60-69 and 70+ and $p=0.006$ in the younger age group, 40-49 years). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

Figure 3 Trends in mortality from sporadic CJD by age: 1970-2000

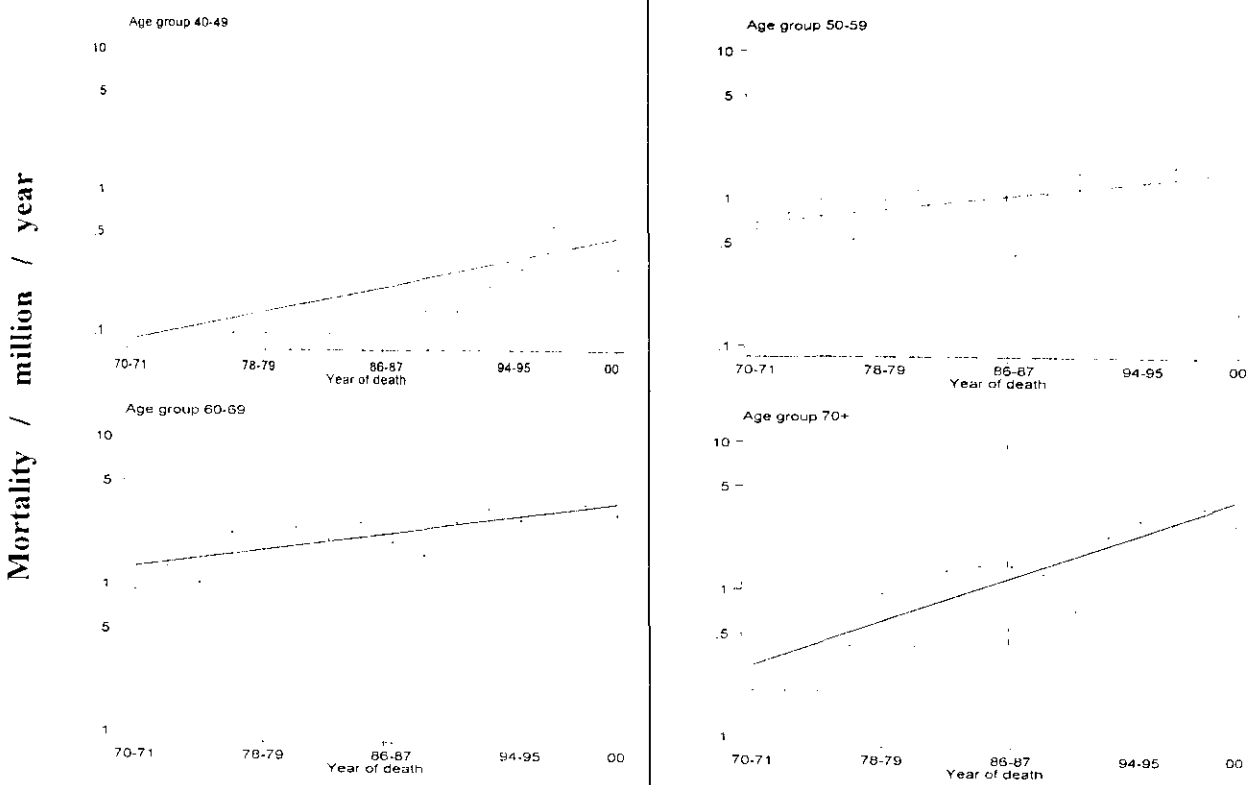


Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged less than 50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 20 per year in the UK in recent years.

Table 2 **Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period**

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	98-99	2000[2]	**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	1	0	**2 (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	9	2	**42 (0)**
50-59	7	9	11	6	11	13	12	9	5	13	18	12	14	20	28	1 (1)	**189 (1)**
60-69	9	13	10	22	17	24	20	28	22	18	30	37	31	35	40	18 (2)	**374 (2)**
70 +	2	2	2	4	9	4	13	16	18	16	9	29	37	35	45	17 (4)	**258 (4)**
Total	**21**	**24**	**25**	**35**	**40**	**45**	**47**	**57**	**49**	**50[3]**	**60**	**81**	**86**	**99**	**124**	**38 (7)**	**881[3] (7)**

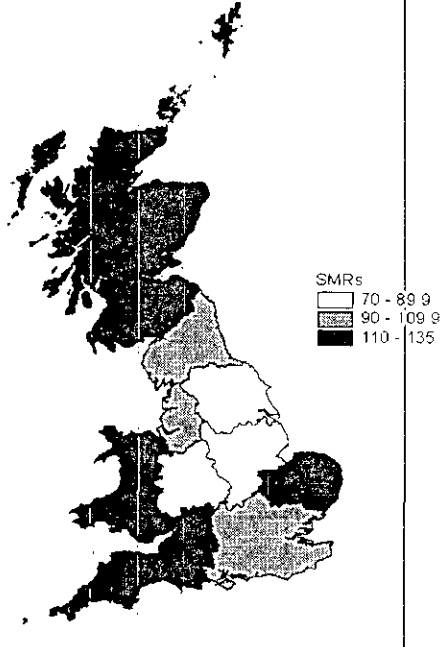
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included

[2] Deaths up to 31st December 2000. Numbers in parentheses indicate additional cases alive on 31st December 2000. Data for 2000 not yet complete.

[3] Total includes one case whose age at death was unknown

Standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st May 1990 to 31st December 2000 were calculated. Figure 4 shows the 10 regions of Great Britain. Northern Ireland has an SMR of 71. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p > 0.2$). Regions of relatively high mortality are East Anglia (SMR=129), the South West (SMR=123) and Wales (SMR=122). Low mortality rates were observed in East Midlands (SMR=81), the West Midlands (SMR=83) and Yorkshire & Humberside (SMR=90). The SMRs for the other five regions all lay between 95 and 112. The highest SMR (129 in East Anglia) arose from 23 cases observed compared with 18 expected, an excess of about 1 case every 2 years. In the South West and Wales the excess numbers of cases were approximately 10 and 6 respectively.

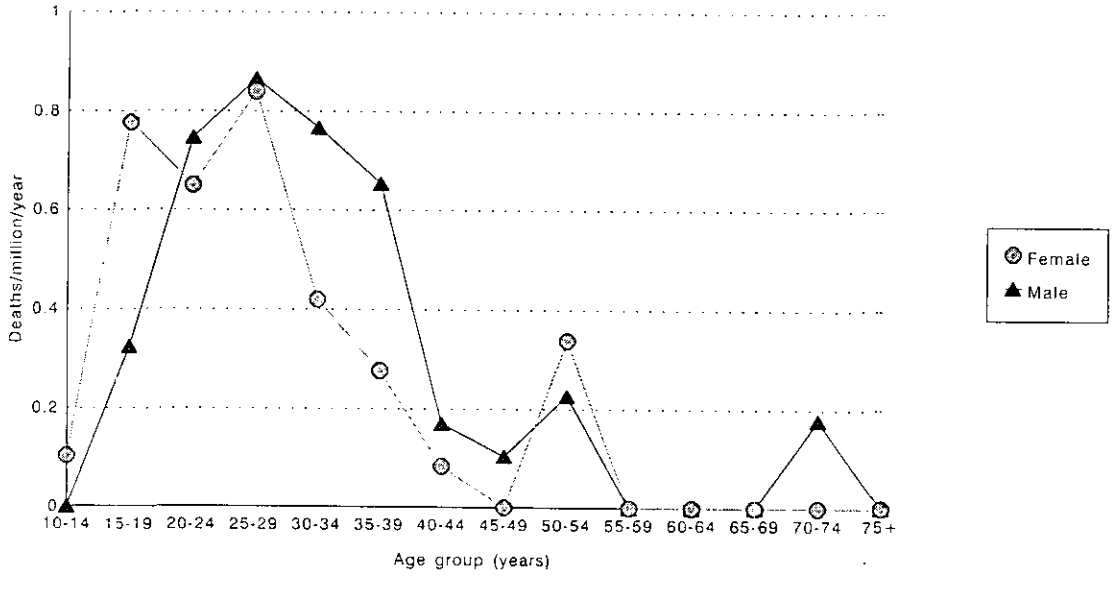
Figure 4 **Standardised mortality ratios (SMRS) by standard region, Great Britain, May 1990 - December 2000**



2.2 Variant Creutzfeldt-Jakob disease

Up to 31st January 2001, 93 cases of definite or probable vCJD had been identified in the UK (75 definite, 2 probable awaiting neuropathological confirmation, 9 probable who did not undergo post mortem and 7 probable cases still alive). Forty-two (45%) of the 93 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 65 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. Up to 1999, the oldest case was 53 years (age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 January 2001 are shown in Figure 5). The median duration of illness was 13 months (range 6-39).

Figure 5 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31 January 2001



Mortality rates calculcated using 1991 Census

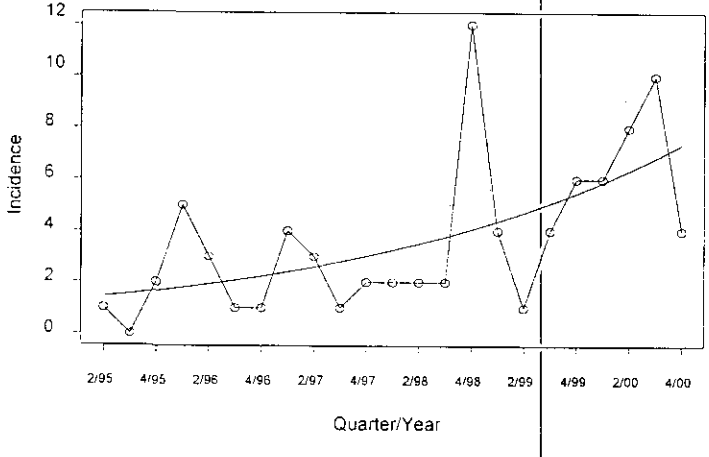
Incidence of vCJD deaths from January 1995 to December 2000

Each quarter the data on vCJD deaths are reviewed in order to investigate trends in the underlying rate at which deaths are occurring. The following analysis reviews the data to the end of December 2000 by which time there was a total of 84 deaths. The data were grouped into quarters and modelled using Poisson regression.

Results for deaths

Figure 6 shows the observed numbers of deaths by quarter with the fitted underlying trend and 95% confidence interval.

Figure 6 Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying trend (__) is given with its 95% confidence limits (...)



The fitted line is log(incidence) = -0.092 + 0.075*quarter. This gives an estimated annual increase of 1.35, 95% CI (1.13 to 1.61) and a p-value for the trend of < 0.001.

The estimate of the current quarterly incidence of deaths is 7.4. Note that it is possible there may be more deaths in the latest quarter which have not yet been reported. The large number of deaths in the fourth quarter of 98 means that the variation by quarter is more than would be expected by

chance, this is accounted for by re-scaling the variance in the model when assessing the significance of the trend.

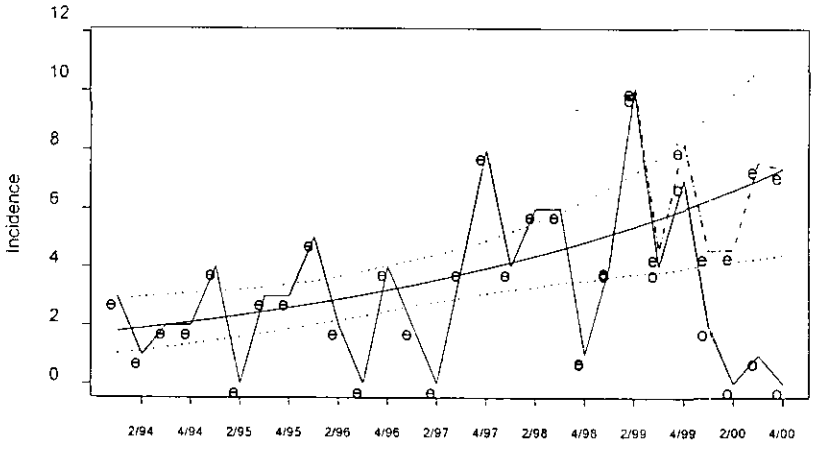
Prediction for deaths in 2001

From the model, if the current trend continues, the predicted total number of deaths for 2001 is 36 with a 95% confidence interval of 21 to 58.

Analysis of onsets and delays to diagnosis

Another analysis was performed in which the incidence of onsets and delay to diagnosis was jointly modelled using Poisson regression. This analysis included 88 cases diagnosed by the end of 2000 and showed an increasing trend in onsets from 1994 to 2000 similar to that found for deaths (Figure 7). The analysis also demonstrated a significant reduction in the delay from onset to diagnosis with an estimated reduction from 14.5 months for onsets in 1995 to 9.5 months for onsets in 2000. The model also estimated that approximately a further 23 onsets will have occurred by the end of 2000 which were not diagnosed by the end of 2000.

Figure 7 Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets Fitted underlying trend*(__) is given with its 95% confidence limits (...)



* includes adjustment for delay from onset to diagnosis

Geographical distribution of variant CJD

Figure 8 shows the geographical distribution, by place of residence at onset, of the 93 cases of vCJD with onset in the UK. Table 3 contains data on the geographical distribution, by place of residence at onset, of the 86 cases who had died by 31 January 2001 along with the mortality rate per million population per annum of each region. This shows that the cases to date have been widely spread geographically.

Figure 8 Geographical distribution of places of residence at onset of symptoms of vCJD cases

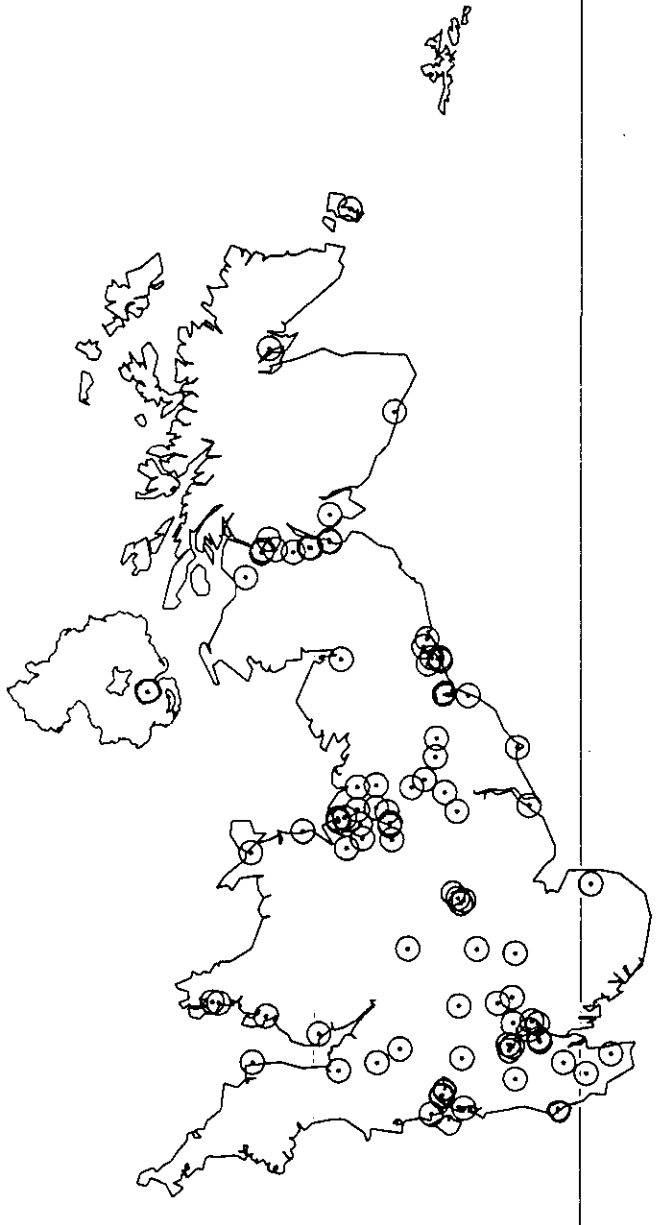


Table 3 Deaths from definite and probable vCJD by region and county of onset: 1 May 1995 - 31 January 2001

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	1	
Cumbria	1	8 (0.45)
Durham	0	
Northumberland	1	
Tyne & Wear	5	
East Midlands		
Derbyshire	0	
Leicestershire	4	
Lincolnshire	0	5 (0.21)
Northamptonshire	1	
Nottinghamshire	0	
South East		
Bedfordshire	0	
Berkshire	0	
Buckinghamshire	0	
East Sussex	0	
Essex	0	
Greater London	8	
Hampshire	5	23 (0.22)
Hertfordshire	2	
Isle of Wight	0	
Kent	3	
Oxfordshire	1	
Surrey	3	
West Sussex	1	
North West		
Cheshire	4	
Greater Manchester	5	14 (0.38)
Lancashire	2	
Merseyside	3	
WALES		
Clwyd	1	
Dyfed	2	
Gwent	0	
Gwynedd	1	
Mid Glamorgan	0	
Powys	0	
South Glamorgan	1	
West Glamorgan	1	
TOTAL FOR WALES		**6 (0.36)**
NORTHERN IRELAND	1	**1 (0.11)**

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
Yorkshire & Humberside		
Humberside	2	
NorthYorkshire	1	
South Yorkshire	2	8 (0.28)
West Yorkshire	3	
East Anglia		
Cambridgeshire	1	
Norfolk	1	2 (0.17)
Suffolk	0	
South West		
Avon	0	
Cornwall	0	
Devon	1	4 (0.14)
Dorset	0	
Gloucestershire	0	
Somerset	2	
Wiltshire	1	
West Midlands		
Hereford & Worcs.	0	
Shropshire	0	
Staffordshire	0	1 (0.03)
Warwickshire	1	
West Mids (Met)	0	
TOTAL FOR ENGLAND		**65 (0.23)**
SCOTLAND		
Borders	0	
Central	0	
Dumfries & Galloway	0	
Fife	1	
Grampian	0	
Highland	1	
Lothian	4	
Strathclyde	7	
Tayside	0	
Islands (Shetland)	0	
Islands (Orkney)	1	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**14 (0.47)**

* Based on 1994 population by region (ONS Regional Trends, 1996 edition) over the 5.75 year period.

Table 4 and Figure 9 show cumulative regional rates of vCJD based on cases' place of residence in 1991 and the population aged 10 years and above at that time. We previously performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The "South" comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East.

Table 4 **Distribution of 91 vCJD cases by standard region of residence on 1st January 1991**

Standard region (in order of latitude of the centre of the region)	Population aged 10 years and above at the 1991 census	Number (cumulative incidence/million) of vCJD cases by place of residence in 1991
Scotland	4,363,684	13 (2.98)
North	2,635,785	8 (3.04)
Yorkshire & Humberside	4,202,051	10 (2.38)
North-West	5,396,333	14 (2.59)
East Midlands	3,444,391	8 (2.32)
West Midlands	4,464,592	3 (0.67)
East Anglia	1,775,687	2 (1.13)
Wales	2,466,669	4 (1.62)
South-East	15,010,650	23 (1.53)
South-West	4,055,268	6 (1.48)
Total	47,815,110	91 (1.90)

Figure 9 Cumulative incidence up to 31st January 2001 of vCJD per million population aged 10 years and above, by place of residence on 1st January 1991

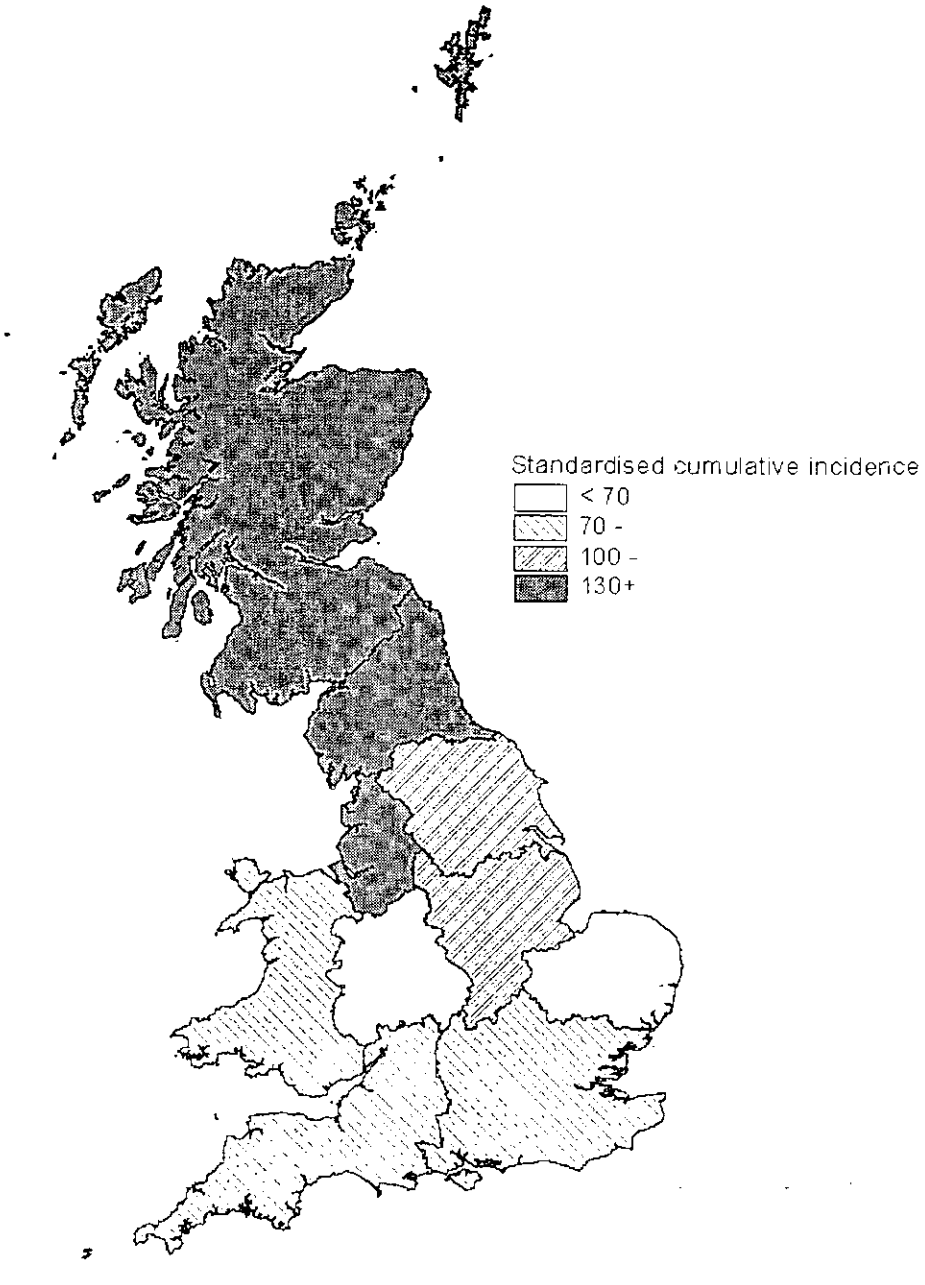


Table 5 shows the distribution of cases between the "North" and the "South" in 1991, distinguishing between those cases included in the previous analysis and those classified as cases subsequently (under an *a priori* hypothesis). The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) appears to have been largely maintained in subsequent cases (rate ratio controlling for age and sex = 1.66; 95% c.i. 0.89, 3.09). Taking all 91 cases together the estimated rate ratio controlling for age and sex is 1.81 (95% c.i. 1.20, 2.74).

Table 5 Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"

Region	**Population aged 10 years and above at the 1991 census**	**Number (rate/million) of vCJD cases by place of residence at 1st January 1991**		
		First 51 cases	Subsequent cases	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	19 (1.14)	45 (2.71)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	21 (0.67)	46 (1.47)
Total (rate ratio[1])	47.8 million	51 (1.94)	40 (1.66)	91 (1.81)

Northern cases were slightly older at onset than southern cases (median of 27 years versus 24 years; p=0.25) and more of them were male (60% versus 48% of southern cases; p = 0.24).

[1] North versus South, adjusted for age and sex

To investigate whether the difference between North and South might be related to socio-economic differences, we examined the Carstairs' index for each case based on their place of residence (enumeration district [ED]) in 1991. The mean Carstairs' score for the cases was -0.41 (95% c.i. –1.02, 0.19), close to the national average (0.0), and to the average conditional on their regional distribution (0.11). The cases were evenly distributed across the five quintiles of the index (data not shown).

Data from the Dietary and Nutritional Survey of British Adults on consumption of those items most relevant to putative transmission of BSE through diet are presented in Table 6. Those items most likely to have contained mechanically recovered meat (MRM) or high titre material from the central nervous system ("burgers and kebabs", "sausages", "meat pies and pastries", "other meat products") show no consistent pattern of higher consumption in the northern regions. While consumption of "meat pies and pastries" appears to be highest in the north, consumption of "burgers and kebabs" and "other meat products" appears highest in the South East.

Table 6 Regional variations in weekly quantities of foods consumed (grams) measured in the period 1986-1987[2]

Type of food	**Mean quantity per person in grams by region**			
	Scotland	Northern, North West, Yorks & Humbs	East Midlands, East Anglia, West Midlands, South West and Wales	South East
Beef and veal	351	342	319	362
Burgers and kebabs	170	166	139	205
Sausages	147	136	142	143
Meat pies and pastries	251	284	243	237
Other meat products	170	201	197	215
Total	1089	1129	1040	1162

[2] Data from the Nutritional Survey of British Adults

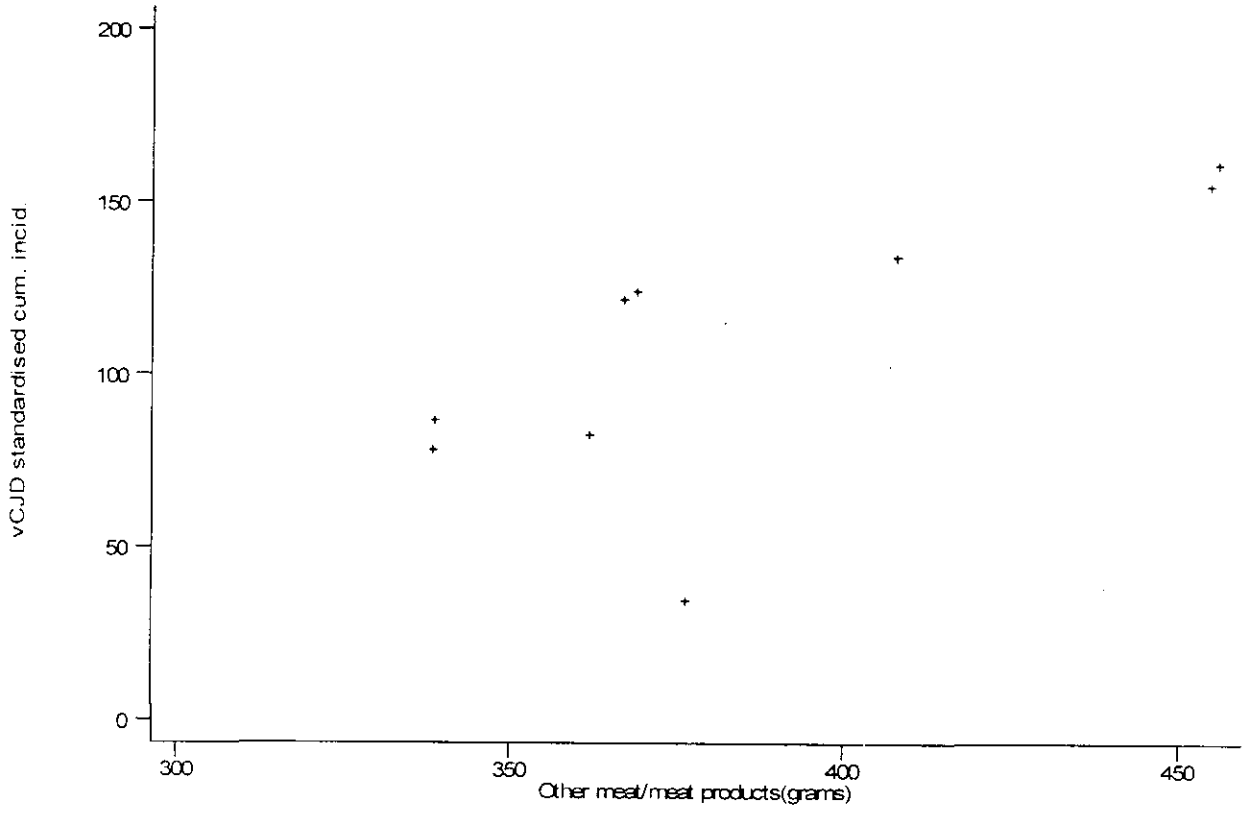
The data on meat consumption published in the Household Food Consumption and Expenditure report for 1988 for the period 1984-1986 are shown in Table 7. Only four categories of meat/meat products were distinguished. "Carcase meat" includes joints, steaks, chops and mince of beef, pork and lamb. The products most likely to have contained bovine MRM or high titre material from the central nervous system fall into the "other meat and meat products" category. There is some evidence of a positive correlation between consumption of "other meat and meat products" and vCJD incidence (Spearman's rank correlation = 0.73; p=0.02) (Figure 10). Interestingly both carcase meat and poultry consumption show some evidence of a negative correlation with vCJD incidence (Spearman's rank correlation coefficients of -0.65 (p=0.06) and -0.62 (p=0.08) respectively), while bacon consumption shows no evidence of a correlation with vCJD incidence (Spearman's rank correlation coefficient = 0.18; p=0.64).

Table 7 Regional variations in weekly quantities of foods brought into the home (grams) measured in the period 1984-1986[3]

	Scotland	North	Yorks & Humbs	North West	East Mids	West Mids	South West	South East/ East Anglia	Wales
Carcase meat	325	362	359	377	373	392	395	382	355
Bacon	102	119	113	121	110	122	89	88	113
Poultry	158	192	174	199	175	212	196	205	191
Other meat and meat products	455	456	369	408	367	376	362	338	339
Total	1040	1129	1015	1105	1025	1102	1042	1013	998

[3] Data from Household Food Consumption and Expenditure: 1988

Figure 10 **Scatterplot of cumulative, age-standardised vCJD incidence against weekly consumption of other meat and meat products (grams) by region (dietary data from Household Food Consumption and Expenditure:1988)**



The spatial scan statistic applied to data at the census enumeration ward level identified a group of five cases in Leicestershire as the "most likely cluster" (P=0.004). No other statistically significant (P<0.05) clusters of cases were identified. In particular, the cases in Kent, which have been the subject of debate, were not identified as a cluster. The total population of Leicestershire at the 1991 census was approximately 870,000, giving a cumulative incidence of vCJD for Leicestershire of about 5.7 per million, compared with an overall cumulative incidence in the UK (excluding Northern Ireland) of 1.7 per million. Four of the five Leicestershire cases lived in the district of Charnwood, with a population in 1991 of about 142,000, giving a cumulative incidence of vCJD for this district of about 28.2 per million. The fifth case lived a couple of km outside Charnwood District and the greatest distance between any two of the cases in 1991 was less than 10km. In other respects, these cases do not appear, at first sight, different from cases from elsewhere in the country. Two were female and the ages at onset ranged from 17 to 33 years. All five cases were reported to have eaten beef products. One had worked as a farm labourer. A summary of the final report of the investigation into the North Leceistershire cluster of vCJD undertaken by Dr Gerry Bryant and Dr Philip Monk can be found on the following website - http://www.leics-ha.org.uk/cjd/cjdbrief.htm.

2.3 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2000, 42 cases of CJD attributable to iatrogenic exposure have been identified, 6 in individuals receiving dura mater implants, 35 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). The mean age at death of the hGH /hGN group was 29 years (with a range of 20-45 years) and for the dura mater cases 43 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.

2.4 Molecular Genetics

Forty cases of familial CJD have been identified since 1970, excluding cases of GSS. Of these, 38 were resident in England and 2 were resident in Wales. Fourteen of the cases had insertions in the coding region of the PrP gene, 11 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI), 1 at codon 117 (Ala-Val) and 1 at codon 210 (Val-Ile). Eleven were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (with a range 38 - 68 years).

Codon 129 distribution in sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD (69% MM, 14% MV, 17% VV) (see Table 8) is consistent with findings from other European countries. There is no evidence ($p > 0.1$) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2000.

Table 8 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2000

Deaths from sporadic CJD	MM (%)	MV (%)	VV (%)
Deaths from 1 May 1990 - 31 December 1995	95 (75)	14 (11)	17 (13)
Deaths from 1 Jan 1996 - 31 December 2000	103 (65)	25 (16)	31 (19)
Total	198 (69)	39 (14)	48 (17)
Genotype distribution for the normal caucasian population pooling data from five studies	(39)	(50)	(11)

Codon 129 distribution in vCJD

All cases for whom genetic data are available (87) were methionine homozygotes at codon 129 of the PrP gene.

2.5 CSF Protein Analysis

A laboratory dedicated to the analysis of cerebrospinal fluid (CSF) was established in the CJDSU in March 2000. The principal role of this laboratory is the analysis of CSF for 14-3-3 and related brain-specific proteins in suspect cases of CJD. The laboratory provides a diagnostic service for the United Kingdom. In addition, the laboratory has received samples from other countries in relation to the European collaborative surveillance projects with which the Unit is involved. Finally, the laboratory is involved in research into CSF proteins in relation to CJD.

In the period from March to December 2000, a total of 201 CSF samples were received and processed by the laboratory. The samples are divided into 3 groups. Firstly, there are samples from patients formally referred to the NCJDSU as suspect CJD cases. Secondly, there is a group of "CSF only referrals". These are CSF samples analysed by the laboratory from patients in the United Kingdom with illnesses that were thought not to be CJD and thus not formally referred as suspect cases. Finally, there is a group of samples from other countries. The details are found in the Table 9.

Table 9 Number and origin of CSF samples received and analysed at the NCJDSU during March 2000 - December 2000

Group	CSF samples	Percentage of total
NCJDSU suspect case referrals	99	49
CSF only referrals	72	36
Non UK samples	30	15
Total	201	100

Table 10 shows the CSF 14-3-3 results in these groups of patients.

Table 10 CSF 14-3-3 results in NCJDSU UK suspect referrals (n=99), March-December 2000

Type of CJD	Diagnostic group as of 31 December 2000 (number of patients)	Positive 14-3-3 / number of valid samples tested	Number of blood stained CSF samples*
Sporadic	Definite (14)	9/11**	4
	Probable (11)	11/11	0
	Possible (8)	0/6	2
	Not CJD (28)	3/27	1
Variant	Definite (6)	4/6	0
	Probable (9)	0/11†	0
	Possible (2)	1/2	0
	Not CJD (14)	0/13	1
Familial	Definite (1)+	1/1	0
	Probable (1)+	1/1	0
	Not CJD (1)	0/1	0
Iatrogenic	Unclassified (1)	1/1	0

* Blood stained CSF samples were not analysed as these samples will give a false positive reaction for 14-3-3.
** One patient had 2 CSF samples taken and analysed, showing one negative and one positive result (see below).
† Two patients each had 2 CSF samples taken and analysed.
+ These patients have a codon 200 mutation.

CSF 14-3-3 was detected in 91% (20/22) of samples from patients with definite and probable sporadic CJD.

One patient with definite sporadic CJD was negative for 14-3-3 in the CSF. The neuropathological features of this case were typical of those found in sporadic CJD who are valine homozygous at codon 129 of the PRNP gene.

A second patient with definite sporadic CJD had 2 samples. The first sample, which was taken early in the course of the disease was negative. The second sample taken 3 months later, was positive. This case was heterozygous (MV) at codon 129 of the PRNP gene and had a relatively long duration illness of 13 months.

Of the 11 probable sporadic cases (classified as probable based on clinical features plus positive 14-3-3), 3 also showed the typical EEG appearances of sporadic CJD (generalised triphasic periodic complexes at approximately one per second). In the remaining 8 cases, EEG did not show the typical EEG appearances of sporadic CJD.

Three patients referred as suspect CJD who turned out to have another illness, were found to be positive for 14-3-3. One of these patients was suffering from paraneoplastic syndrome, the second from an encephalitis, while the third patient had no certain diagnosis. However, this last patient's clinical condition improved, excluding the possibility of sporadic CJD.

CSF 14-3-3 was detected in 67% (4/6) of patients with definite variant CJD. However, in the 9 cases classified as probable variant CJD, none had a positive 14-3-3. This may be explained by the timing of the CSF sample.

CSF 14-3-3 was not detected in any of the patients initially referred as suspect variant CJD who later turned out to have another illness.

Of the 72 CSF samples from non-suspect cases, 5 were blood stained and therefore unsuitable for analysis, 3 were positive for 14-3-3 and the remainder did not have detectable 14-3-3. Of the 3 positive 14-3-3 cases, one had Herpes Simplex encephalitis and 2 had encephalitis of unknown cause.

In conclusion, the analysis of CSF 14-3-3 has a high degree of sensitivity and specificity for the diagnosis of sporadic CJD, and has enabled patients who would have been previously diagnosed as possible CJD to be classified as probable. In particular, a diagnosis of probable sporadic CJD was made in 8 patients (during the period March-December 2000) who would not have fulfilled the current WHO and EU criteria due to either the absence of typical EEG changes or because an EEG had not been performed.

2.6 National Care Co-Ordinator

The role of the co-ordinator is to provide advice on all forms of CJD to the patient, their family and professional carers, including information on the clinical features, diagnostic procedures and prognosis. The co-ordinator assists with the co-ordination of the care locally, working closely with and supporting the identified key worker who has responsibility for ensuring that the needs of the patient and the family are met. Regular case conferences are encouraged, which the co-ordinator attends when possible in order to assist with the assessment and reassessment of evolving needs. Having experience with families previously affected by this disease allows the co-ordinator to provide information on successful interventions, which may be helpful for other families.

When a referral has been made to the unit of a suspect case of CJD, the co-ordinator makes direct contact with the family and arranges to meet with them within two weeks. Thereafter the co-ordinator meets with the patient and the family on a regular basis, depending on need, to provide support and is available by telephone between visits. Support continues after the patient dies.

Since the establishment of this post in June 2000, the co-ordinator has had contact with 20 families affected by CJD or vCJD and has visited each on a regular basis. Currently there are nine patients that are affected by vCJD and the co-ordinator has contact with each family.

2.7 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply.

Methods

vCJD cases (definite and probables) are notified to the UKBS by NCJDSU; a search establishes whether any have acted as donors. Donation records are checked and all components traced through hospital records. Details of recipients are forwarded to NCJDSU for subsequent checking.

In the reverse procedure, patients with vCJD reported to have received blood transfusions are identified by NCJDSU and notified to UKBS. Details of transfusions are traced through hospital records and relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking.

Results

For vCJD cases, 15 were reported to have been blood donors. To date, only 10 have been traced at blood centres, and 8 of these had donated blood, with a resulting 48 blood components. It has been established that 22 components were transfused to named recipients.

In the reverse study, 8 vCJD cases were reported to have received blood transfusions. Checks revealed that 2 were not transfused, 2 had transfusions which predated available records and 4 had records of transfusion which could be traced. To date, these 4 received 117 blood components of blood, corresponding to 111 named donors (one patient received 103 components). The donors of two components are not traceable and checking is still incomplete on 4 components.

Conclusion

No donors or recipients identified in the study through the tracing of donation and transfusion records appear in the NCJDSU register as cases. Further data on vCJD cases, to define time interval between blood donation and development of disease are being accumulated.

(Collaborators on this project: Dr P.E. Hewitt and Dr C.A. Llewelyn).

2.8 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an expert neurological advisory group of six paediatric neurologists which allocates the cases to a diagnostic category[4].

[4] Verity CM, Nicoll A, Will RG, Devereux G, Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 2000; 356: 1224-1227.

After 45 months surveillance, 1082 patients with suspected PIND have been reported. Among them were four cases of vCJD; three definite and one probable. Three were reported in 1999 and one in 2000. One girl was aged 12 at onset - the youngest ever case of vCJD. No other children with the clinical features of vCJD were identified. The expert group has discussed 785 cases, of which 435 have a confirmed underlying cause other than vCJD, being categorised into 89 known neurodegenerative diseases.

(Collaborators: Dr C. Verity, Dr A. Nicoll, Ms G. Devereux).

SECTION

3

3. Case-Control Study

Methods

Since May 1990, a case-control study of CJD has been carried out in the UK to investigate potential risk factors. 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 residential, occupational, dietary and medical histories. Up until 1997, for each suspect case, an age and sex-matched inpatient at the same hospital was identified as a control. At the end of 1997 the design of the study was changed. In addition to hospital controls for variant cases and instead of hospital controls for sporadic cases, community controls are recruited, matched for sex and age ± 4 years, through general medical practices (up to 4 for each case of vCJD and one for each case of sporadic CJD). Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. When possible, a relative of the same degree as for the case is interviewed using the standard questionnaire. If this is not possible the control is interviewed directly. Ethical clearance for the revised study design was received from the Multi-Centre Research Ethics Committee for Scotland in October 1998. Subsequently, Local Research Ethics Committee (LREC) approval has been obtained for each general practice in the study.

Following LREC approval, the complex and time-consuming process of control recruitment commenced. As of March 2001, letters have been sent to 79 GPs to ask them to participate in the study and forty-four practices have been visited. Letters have been sent to 723 potential controls by their GP describing the study and asking them to agree to be approached directly by the NCJDSU. One hundred and seventy- two (24%) of these individuals have replied, of whom 127 (74%) agreed to be contacted by the NCJDSU. Of those written to by the NCJDSU (n=122), 88 (72%) have replied. Eighty-seven have consented to take part in the study and have nominated a relative for interview. Sixty-nine relatives have agreed to take part in the study, of whom 67 have been interviewed.

Variant CJD

By the end of 2000, risk factor questionnaires for 53 community controls and 60 hospital controls had been completed (relating to 25 and 60 vCJD cases, respectively). Of the vCJD cases included in the analyses, 18 have both community and hospital controls, seven have only community controls and 42 have only hospital controls.

Comparisons of cases with controls have been performed separately for the community and hospital controls, because of the potential heterogeneity of these two control groups with respect to factors under investigation.

3.1 Medical risk factors for vCJD

Analysis was restricted to cases with matched community controls because of the potential for bias in using hospital controls to investigate medical risk factors.

Community controls

Seventy-two percent of community controls were reported to have had some sort of operation/surgical procedure in the past compared with 64% of cases (Table 11). There is no evidence to suggest that particular operations/surgical procedures are associated with increased risk of vCJD (Table 11). However, the confidence intervals around these odds ratio estimates are wide. These findings should not be interpreted as evidence that transmission via surgery has never, or could never, occur.

Table 11 **Reported operations/surgical procedures for 25 cases of variant Creutzfeldt-Jakob disease and 53 community controls.**

Type of operation/ surgical procedure	% of cases (n = 25)	% of controls (n= 53)	Odds ratio (95% CI), p value (based on matched cases and controls)
Any operation	64	72	0.9 (0.3, 2.5), 0.8
Neurological operation	0	4	(-, 5.3)
Eye operation	0	6	(-, 9.2)
Ear operation	0	6	(-, 5.3)
Orthopaedic operation	8	8	1.4 (0.2, 7.5), 0.7
Abdominal operation*	12	19	0.4 (0.1, 1.9), 0.2
Tonsillectomy	8	17	0.5 (0.1, 2.8), 0.4
Appendicectomy	4	6	0.5 (0.0, 4.5), 0.5
Other	56	60	1.0 (0.4, 3.0), 0.9

*Includes appendicectomy

Blood transfusion

3 of the 25 cases were reported by relatives to have had a history of blood transfusion compared with 3 of the 53 community controls, (O.R. 2.5 (0.5, 12.7), p= 0.3).

3.2 Dietary risk factors for vCJD

Community controls

The reported consumption of various different meats and meat products by cases and controls in the period since 1980 (except for one case where the period is from 1985 due to a change in the questionnaire and one case where the relative could only answer from 1993 onwards) is shown in Table 12.

Almost all cases and community controls were reported to have eaten beef (joints, steaks, stews etc.). Eighty-eight percent of cases and 96% controls ate sausages (p=0.14), 79% and 90% ate burgers (p=0.13) and 81% and 83% ate meat pies (p=0.8), respectively. Only two controls were reported to have eaten brain. No cases or controls reported having eaten eyes. More cases (52%) than controls (31%) were reported to have eaten black pudding (p=0.04). However, it should be remembered that because of multiple statistical testing, one positive test out of 22 tests may be expected by chance.

Table 12 **Reported consumption of different types of meat from 25 cases[1] of variant Creutzfeldt-Jakob disease and 53 community controls.**

Type of foodstuff	% of cases (n =25, unless indicated)	% of community controls (n =53, unless indicated)	Odds ratio (95% C.I.); p-value (based on matched cases and controls)
Beef	100 (24)	96 (52)	(0.1, -)
Sausages	88	96 (52)	0.3 (0.0, 1.6); 0.14
Burgers	79 (24)	90 (51)	0.3 (0.1, 1.4); 0.13
Meat pies	81 (21)	83	0.8 (0.2, 3.1); 0.8
MRM[2]	92	94	0.4 (0.1, 3.2), 0.4
Venison	28	26	1.2 (0.3, 4.2); 0.8
Veal	20	19	1.0 (0.3, 4.0); 1.0
Brain	0	4	(-, 10.2)
Liver	60	65 (52)	0.7 (0.3, 2.0); 0.6
Kidney	36	23	2.6 (0.8, 9.1); 0.12
Sweetbreads	0 (24)	4	(-, 5.3)
Lamb	84	93	0.5 (0.1, 2.0); 0.3
Pork	100	96	(0.0, -)
Chicken	96	96	0.9 (0.1, 9.8); 0.9
Faggots	36 (22)	21	2.3 (0.7, 8.0); 0.18
Tripe	4	8	0.8 (0.1, 7.9); 0.8
Liver sausage	39 (19)	49	0.4 (0.0, 3.3); 0.4
Haggis	40	38	1.0 (0.3, 3.7); 0.9
Steak tartare	0 (13)	2	-
Cheese	96	96 (52)	1.0 (0.1, 11.9); 1.0
Cows milk	100	98 (52)	(0.0, -)
Black pudding	52	31 (52)	3.4 (1.0, 11.5); 0.04

[1] In one case the dietary history was recorded from 1985 onwards and in another from 1993 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

The reported frequency of consumption of the selected food items shown in Table 12 (except cows' milk) by cases and community controls were compared; a selection of which are shown in Table 13. There was weak evidence that the reported frequency of consumption of sausages, faggots and black pudding was greater for cases compared with controls (p= 0.08, 0.07 and 0.06, respectively). There was no evidence that the reported frequency of consumption of beef, meat pies, burgers or products which might have contained mechanically recovered meat (MRM) (derived from the combined frequencies of eating burgers, meat pies and sausages) differed between cases and controls (p= 0.2, 0.2, 0.9 and 0.3, respectively).

Table 13 Reported frequency of consumption of food items from 25 vCJD cases[1] compared with 53 community controls

Foodstuff eaten	Frequency	% of cases (n =25, unless indicated)	% of community controls (n =53, unless indicated)	Odds ratio (95% C.I.); (based on matched cases and controls)	p-value for trend
Beef	≤ 1 per month	25 (24)	29 (52)	1.0	0.2
	1 per week	21	44	0.4 (0.1, 1.8)	
	> 1 per week	54	27	1.7 (0.5, 6.2)	
Sausages	≤ 1 per month	40	56 (52)	1.0	0.08
	1 per week	32	36	1.4 (0.4, 4.6)	
	> 1 per week	28	8	5.3 (0.9, 30.9)	
Burgers	≤ 1 per year	21 (24)	24 (51)	1.0	0.9
	Several times per year to 1 per month	42	37	1.0 (0.2, 4.4)	
	≥ 1 per week	37	39	0.9 (0.2, 4.6)	
Meat pies	≤ 1 per year	29 (21)	25	1.0	0.2
	Several times per year to 1 per month	38	28	1.3 (0.3, 5.3)	
	≥ 1 per week	33	47	0.3 (0.1, 1.6)	
MRM[2]	≤ 2 per month	16	33 (n=51)	1.0	0.3
	2> & <8 per month	36	28	2.5 (0.7, 9.5)	
	≥ 8 per month	48	39	2.1 (0.5, 8.8)	
Faggots	Never	64 (22)	79	1.0	0.07
	≤1 per year	9	11	1.1 (0.2, 6.0)	
	> 1 per year	27	9	5.1 (0.9, 28.3)	
Black pudding	Never	48	69 (52)	1.0	0.06
	≤ 1 per year	20	12	3.5 (0.6, 18.5)	
	> 1 per year	32	19	3.4 (0.9, 13.5)	

[1] In one case the dietary history was recorded from 1985 onwards and in another from 1993 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

Hospital controls

Table 14 shows the reported consumption of various meats and meat products by cases and hospital controls since 1980 (except for one case and one control where the period is from 1985 due to a change in the questionnaire).

As for the comparison with community controls, almost all cases and hospital controls were reported to have eaten beef. Higher proportions of cases than hospital controls were reported to have consumed burgers (p=0.02) and meat pies (p=0.08). Almost all cases and controls were reported to have consumed products likely to have contained MRM (burgers, meat pies and sausages). There was no evidence that reported consumption of any of the other meat products shown in Table 14, including black pudding (p=0.7), was associated with increased risk of vCJD.

Looking at the frequency of consumption (Table 15), cases were reported as having eaten two foodstuffs (out of 14 foodstuffs that were analysed) more frequently than their matched hospital controls: beef, p=0.008 and burgers, p=0.002. Some foodstuffs were so rarely eaten that an analysis of frequency of consumption could not be performed. Forty-five percent of cases were reported to have eaten beef more than once per week compared with 23% of hospital controls; and 66% of cases were reported to have eaten burgers at least once per week compared with 41% of hospital controls. There was no evidence that the reported frequency of consumption of sausages or meat pies differed between cases and hospital controls (p=0.6 and 0.1 respectively). There was weak evidence that reported consumption of products likely to contain MRM was more frequent among cases than among hospital controls (p=0.07).

Table 14 **Reported consumption of different types of meat from 60 cases[1] of variant Creutzfeldt-Jakob disease and 60 hospital controls[1].**

Type of foodstuff	% of cases (n =60, unless indicated)	% of hospital controls (n =60, unless indicated)	Odds ratio (95% C.I.); p-value (based on matched cases and controls)
Beef	100	93	(0.7, -)-
Sausages	97	92	2.5 (0.5, 12.9), 0.3
Burgers	97 (58)	79 (58)	6.0 (1.3, 26.8), 0.02
Meat pies	96 (51)	85 (52)	4.0 (0.8, 18.8), 0.08
MRM[2]	100	95	(0.4, -)
Venison	22	27	0.7 (0.3, 1.8), 0.5
Veal	13	27	0.5 (0.19, 1.14), 0.10
Brain	0	5	(-, 2.4)
Eyes	0 (59)	5	(-, 2.4)
Liver	58	70	0.5 (0.2, 1.3), 0.15
Kidney	32	39 (59)	0.7 (0.3, 1.5), 0.3
Sweetbreads	2	2 (59)	1.0 (0.1, 16.0), 1.0
Lamb	95	88	3.0 (0.6, 14.9), 0.18
Pork	98	92	5.0 (0.6, 42.8), 0.14
Chicken	98	97	2.0 (0.2, 22.1), 0.6
Faggots	38 (53)	30 (53)	1.6 (0.7, 3.9), 0.3
Tripe	5	8	0.6 (0.1, 2.5), 0.5
Liver sausage	51 (37)	44 (41)	1.4 (0.6, 3.4), 0.5
Haggis	22	23	0.9 (0.3, 2.3), 0.8
Steak tartare	0 (38)	0 (41)	-
Cheese	95	98	0.3 (0.0, 3.2), 0.3
Cows milk	100	98	(0.0, -)
Black pudding	41 (59)	45	0.8 (0.4, 1.9), 0.7

[1] In one case and one control the dietary history was recorded from 1985 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

Table 15 Reported frequency of consumption of food items from 60 cases[1] compared with 60 hospital controls[1]

Foodstuff Eaten	Frequency	% of cases (n =60, unless indicated)	% of hospital controls (n =60, unless indicated)	Odds ratio (95% C.I.); (based on matched cases and controls)	p-value
Beef	≤ 1 per month	22	40	1.0	0.008
	1 per week	33	37	1.7 (0.6, 5.0)	
	> 1 per week	45	23	4.6 (1.5, 14.5)	
Sausages	≤ 1 per month	33	35	1.0	0.6
	1 per week	37	40	0.9 (0.4, 2.2)	
	> 1 per week	30	25	1.4 (0.5, 3.9)	
Burgers	≤ 1 per year	5 (58)	26 (58)	1.0	0.002
	Several times a year to 1 per month	29	33	4.5 (1.0, 21.3)	
	≥ 1 per week	66	41	11.3 (2.2, 57.8)	
Meat pies	≤ 1 per year	14 (51)	23 (52)	1.0	0.1
	Several times a year to 1 per month	39	37	2.1 (0.6, 7.4)	
	≥ 1 per week	47	40	3.0 (0.8, 10.6)	
MRM[2]	≤ 2 per month	8	17	1.0	0.07
	2> & <8 per month	22	28	1.5 (0.4, 5.7)	
	≥ 8 per month	70	55	2.8 (0.8, 9.5)	

[1] In one case and one control the dietary history was recorded from 1985 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

Summary

In summary, more cases than hospital controls were reported to have eaten burgers and to have eaten them more frequently. The majority of cases and hospital controls were reported to have eaten beef, with cases reported as having eaten it more frequently. However, a large number of statistical comparisons were performed, increasing the probability of observing some "statistically significant" associations, which reflect nothing but chance.

In addition to the problem of false positive findings arising by chance, there is also considerable scope for recall bias with respect to dietary histories. In order to examine this possibility, cases (n=90) were compared with a group of controls (n=31), who were people referred to the NCJDSU with suspect vCJD who were subsequently determined to have an alternative

diagnosis. Cases were reported to have eaten beef and burgers more frequently than controls. However, no statistically significant differences were found between cases and controls in the frequency of consumption of beef, burgers, sausages, meat pies or MRM containing products (p= 0.5, 0.1, 0.6, 0.7, 0.9 respectively) (Table 16).

Table 16 Reported frequency of consumption of food items more than once a week from 90 vCJD cases[1] compared with 31 controls[1]

Foodstuff eaten	Frequency	% of cases (n= 90)	% of controls (n= 31)	Odds ratio (95% C.I.)	p-value
Beef	≤ 1 per month	22	26	1.0	
	1 per week	34	39	1.0 (0.3, 2.9)	0.5
	> 1 per week	44	35	1.4 (0.5, 4.1)	
Burgers	≤ 1 per year	13	24	1.0	
	Several times a year to 1 per month	29	31	1.8 (0.5, 6.0)	0.1
	≥1 per week	59	45	2.5 (0.8, 7.7)	
Sausages	≤ 1 per month	40	32	1.0	
	1 per week	34	42	0.6 (0.3, 1.7)	0.6
	> 1 per week	26	26	0.8 (0.3, 2.3)	
Meat pies	≤ 1 per year	17	22	1.0	
	Several times a year to 1 per month	33	30	1.4 (0.4, 5.0)	0.7
	≥ 1 per week	49	48	1.3 (0.4, 4.1)	
MRM[2]	≤ 2 per month	12	14	1.0	
	> 2 and < 8 per month	21	21	1.2 (0.3, 5.0)	0.9
	≥ 8 per month	67	66	1.1 (0.3, 4.0)	

[1] In 5 cases and 5 controls the dietary history was recorded from 1985 onwards. In the remainder it was taken from 1980.

[2] MRM - mechanically recovered meat- burgers, meat pies & sausages used in this analysis

It is possible, therefore, that the differences observed between cases and hospital and community controls with regard to the consumption of certain food items result from recall bias.

The recent investigation of the cluster of five cases in Leicestershire by the local Public Health Department has reported an association of risk of vCJD with meat preparation techniques in local butchers' shops. The Leicestershire findings are not incompatible with the absence of a convincing association with diet in the national study. The national study has, so far, focussed on trying to identify particular food items that might have carried a high risk of infection. The Leicestershire study suggests that in that area it was not necessarily particular food items that were associated with risk of vCJD, but the circumstances in which those items were prepared. The Leicestershire findings provide us with a specific hypothesis that needs to be examined on a wider scale.

3.3 Occupation and variant CJD

Community and Hospital controls

Tables 17 and 18 compare the proportion of cases and matched controls that were reported as having ever worked in an occupation considered to be 'at risk' for vCJD. There is no evidence that any of the occupations considered are associated with increased risk of vCJD.

Table 17 Occupation of 24 vCJD cases compared with 53 community controls

Type of occupation	% of cases (n=24)	% of community controls (n=53)	Odds ratio (95% C.I.), p value (based on matched cases and controls)
Medical/ paramedical/ nursing/ dentistry	4	13	(-, 3.3)
Animal laboratories	0	0	-
Pharmaceutical laboratories	0	6	(-, 8.0)
Other research laboratories	0	2	(-, 117.0)
Animal farming/ veterinary medicine	8	0	(0.7, -)
Meat industry	8	6	1.3 (0.2, 8.4), 0.7
Catering industry	33	28	1.1 (0.4, 3.0), 0.9
Other involving animal products	4	4	1.3 (0.1, 14.5), 0.8

Table 18 Occupation of 60 vCJD cases compared with 60 hospital controls

Type of occupation	% of cases (n=60)	% of community controls (n=60)	Odds ratio (95% C.I.), p value (based on matched cases and controls)
Medical/ paramedical/ nursing/ dentistry	5	13	0.4 (0.1, 1.7), 0.2
Animal laboratories	0	0	-
Pharmaceutical laboratories	0	0	-
Other research laboratories	0	0	-
Animal farming/ veterinary medicine	5	7	0.8 (0.2, 3.4), 0.7
Meat industry	5	13	0.4 (0.1, 1.7), 0.2
Catering industry	25	21	1.3 (0.6, 2.8), 0.5
Other involving animal products	3	5	0.3 (0.0, 3.2), 0.3

3.4 Conclusion

To date, we have not observed any evidence of an increased risk of vCJD associated with a reported previous history of surgical procedures or employment in an occupation which might have led to exposure to the BSE/vCJD agent. Some differences in reported diets were observed between cases and controls. These differences need to be interpreted with great caution given the number of statistical comparisons performed and the potential for recall bias to affect interviewees' responses. The evidence for a link between diet and risk of vCJD from this study is less than compelling.

Continued recruitment of cases and matched community controls over time will enable us to make stronger statements with regard to the presence/absence of risk associated with surgical procedures and occupation in the future. The interpretation of the dietary results may become clearer as the number of individuals suspected of having, but then shown not to have, vCJD increases. In addition, the results from the investigation of a cluster of cases in Leicestershire suggest a precise mechanism through which individuals may have been exposed to the BSE agent: namely, through consumption of beef carcass meat prepared in the same location and using the same instruments as those used to split cattle heads and remove their brains. It will be important to investigate the butchering practices to which cases elsewhere in the country were exposed, in order to determine what proportion of cases might be explained by this mechanism.

SECTION

4

Neuropathology

4.1 Statement of Progress

The neuropathology laboratory in the NCJDSU continues to maintain a high workload in terms of both diagnostic and research activities, including the work of the Protein Laboratory. The Neuropathology Laboratory has maintained close links with other related centres in the UK and overseas and many scientific, technical and medical visitors have joined us for short periods of attachment for specialist training purposes. In addition to the routine surveillance and diagnostic work on CJD, the laboratory plays a major role in the National Retrospective Review of CJD and Related Disorders, and a retrospective study to detect abnormal PrP in anonymised specimens of appendix and tonsil tissues. The autopsy rates for sporadic and variant CJD have been maintained at a high level, and through close collaborations with regional pathology centres a high post mortem referral rate for suspected CJD cases has been maintained in 2000. The findings in the Alder Hey inquiry have raised questions concerning the use and retention of autopsy tissues and organs for diagnostic and research purposes: the Neuropathology Laboratory has not received any complaints in this respect and continues to provide accurate information in terms of diagnosis to clinicians and relatives. A small number of relatives have requested that tissues removed at autopsy should be returned for burial and/or cremation and this has been complied with in a timely fashion. We are most grateful to all the neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of the NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

4.2 Surveillance and Workload during 2000

A detailed breakdown of laboratory activities is summarised in Table 19. These demonstrate that there continues to be an increase in the number of cases referred to the laboratory both from the UK and overseas, with a significant increase in the numbers of vCJD cases referred for diagnosis. As in previous years, the most frequent alternative diagnosis for sporadic CJD is Alzheimer's disease, with dementia with Lewy bodies as the second most common diagnosis. In addition to prospective surveillance material, the National Retrospective Review has identified a number of cases which were diagnosed in the UK since 1990, all but one of which had previously been referred to the clinical surveillance arm of the NCJDSU. The National Retrospective Review strengthens the current surveillance project in addition to providing important information in its retrospective component.

With regard to the diagnostic process and internal audit it should be emphasised that cases studied both in the Protein Laboratory and in the Neuropathology Laboratory are diagnosed "blind" to each others findings. This is particularly important in the study of sporadic and variant CJD, particularly in atypical cases of sporadic CJD with a young individual. Each case referred from another centre is returned with duplicate sections to the referring pathologist who is then able to review the case in their own laboratory and discuss the findings with the Neuropathology Laboratory.

Table 19 Breakdown of Laboratory Activities: Period 1st January 2000 – 31st December 2000

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
No evidence of CJD (no alternative diagnosis) *	21	28
Iatrogenic CJD (GHT)	0	5
Gerstmann-Sträussler-Scheinker	0	0
Fatal Familial Insomnia	0	0
Sporadic CJD	36	46
Familial CJD	1	
vCJD	24	14
Peripheral Organs	1	
Other †	10	11
Alzheimer's disease	9	10
Dementia with Lewy Bodies	4	4
Research Project (ocular material)	0	3
Research Project (National retrospective review post-1990)	18	0
REFERRED CASES (EU)		
Confirmed CJD	11	9
vCJD	1	1
GSS	1	0
Other	2	2
REFERRED CASES (ROW)		
Confirmed CJD	4	1
Other	1	1
TOTAL NUMBER OF CASES	**144**	**135**

NOTES:

† Other:

Non specific encephalopathic features in basal ganglia and thalamus	1	Infarction + adenocarcinoma of pancreas	1
Motor Neurone Disease	1	Encephalopathy with vascular sclerosis	1
Paraneoplastic syndrome	1	Vasculitis involving meninges	1
Progressive Multifocal Leucoencephalopathy	1	Right cerebral infarct + small cell carcinoma	1
Corticobasal Ganglionic Degeneration	1	Normal Pressure Hydrocephalus	1

* Material supplied is insufficient for an alternative diagnosis

Abbreviations:
GHT- Growth Hormone Therapy; EU - European Union; ROW - Rest of World

4.3 Protein Laboratory

The prion protein laboratory in the NCJDSU was established in June 1998. The 1999 Annual Report covered the activities of the laboratory from June 1998 - 1999. This report is therefore the first to cover a single calendar year (2000).

Protein Laboratory Aims

1. Integration of Western blot analysis into the NCJDSU repertoire of differential diagnostic tests for CJD and its subtypes, with particular reference to vCJD.
2. Research into pathogenesis and phenotypic variation of CJD.
3. Participation in the development of novel diagnostic tests for vCJD.

Western Blot Analysis of CNS Tissue

The classification of proteinase K resistant prion protein (PrP^{res}) isotypes found in the brains of patients suffering from CJD has proved controversial with the debate centering on the possible molecular sizes of the non-glycosylated PrP^{res} protease resistant PrP protein. This is an important issue since PrP isotypes may equate to "strains" of the infectious agent accounting for phenotypic variation within and between forms of CJD. Our results dictate that we adopt the nomenclature of Type 1 (21kDa) and Type 2 (19kDa) PrP^{res} isotypes. Further classification is possible on the basis of the proportion of the three glycoforms (di-, mono-, and non-glycosylated PrP) present in protease treated brain extracts. The defining characteristic of PrP^{res} from cases of vCJD, namely the predominance of diglycosylated PrP^{res} is referred to by us as Type 2B.

Analysis of all suspected CJD cases referred to the unit (where frozen brain tissue is available) is now routinely carried out (from frontal cortex where possible) as part of the ongoing surveillance program in the UK. The breakdown of new UK cases analysed in 2000 is considered according to final diagnosis as follows (Table 20):

Table 20 Breakdown of cases analysed in 2000

Diagnosis	*Type*		*PrP^{res} +ve CNS*
CJD	Sporadic		21/21
	Variant		13/13
	Familial (E200K)		1/1
	Other	Alzheimer disease	0/6
		Lewy body dementia	0/2
		Other	0/12

PrP^{res} positivity on Western blot analysis accurately distinguishes between CJD whether sporadic, variant or familial (35/35) and neurological diseases with an alternative final diagnosis (0/20). These cases include the analysis of five brain biopsy samples, one of which received a diagnosis of CJD (sporadic type).

Since sporadic CJD is the major differential diagnosis for vCJD and these two classes represent the majority of cases examined, they are considered further. The PrP^{res} isotype determined by Western blotting is shown in conjunction with the *PRNP* codon 129 status, which is known to modify disease susceptibility and phenotype. Of the 34 PrP positive sporadic CJD and vCJD cases, unequivocal isotype classification could be made in 31 cases. Of these the codon 129 status is known in 25 cases and the isotype / genotype distribution is shown below (Table 21):

Table 21 Isotype/genotype breakdown of CJD cases analysed in 2000

Diagnosis	**129**	**Type 1**	**Type 2A**	**Type 2B**	**Total**
sporadic CJD	M/M	6	2	0	8
	M/V	0	2	0	2
	V/V	0	2	0	2
Total		6	6	0	12
vCJD	M/M	0	0	13	13
	M/V	0	0	0	0
	V/V	0	0	0	0
Total		0	0	13	13

These results demonstrate isotypic and genotypic diversity in sporadic CJD in the UK with the majority of sporadic CJD cases being methionine homozygotes but with equal representation of cases with type 1 PrP^{res} and cases with type 2 PrP^{res}.

Material from five cases of sporadic CJD were received for analysis in 2000 from outwith the UK. Four of these were from Finland and one from Eire and all five had type 1 PrP^{res}.

The three UK cases of sporadic CJD that could not be accommodated within the classification system were problematic in that type 1 and type 2 PrP^{res} were both detected in samples taken from cerebral cortex. Two further cases with both type 1 and type 2 PrP^{res} present in the brain were identified during retrospective analysis of cases reported in 1999. The co-existence of type 1 and type 2 PrP^{res} is not restricted to any one codon 129 genotype with examples found in methionine and valine homozygotes and a heterozygote. While the contention that isotype/genotype groups represent distinct clinico-pathological entities of sporadic CJD may remain substantially correct, the existence of more than one PrP^{res} type in individual brains of some patients with sporadic CJD is puzzling and requires further study.

In contrast to sporadic CJD, vCJD remains stereotyped, with all cases thus far examined being methionine homozygotes and having a uniform 2B PrP^{res} isotype irrespective of the area of the brain sampled (year 2000, 13/13). Densitometric analysis of glycoform ratios is ongoing and has provided convincing quantitative evidence that glycoform ratio can be used to distinguish vCJD from the vast majority of cases of other forms of CJD. There are however a number of caveats to this, of which we had direct experience: First, regional glycoform ratio variation has been noted in sporadic CJD (1/5 cases where 17 regions were assayed). Second, a Dutch case of sporadic CJD in a codon 129 valine homozygote has been found to have a glycoform ratio resembling vCJD (see Annual Report for 1999). Third, the familial CJD (E200K) case analysed this year had a 21kDa non-glycosylated PrP^{res} and the glycoform ratio similar to that associated with vCJD (i.e. type 1B). These considerations argue for the cautious integration of Western blot results into CJD diagnosis.

Western Blot Analysis of Peripheral Tissues

The possible presence of CJD infectivity in peripheral tissues of individuals with preclinical CJD presents a risk to public health. It is therefore important to determine the tissue distribution of

PrP^{res} as a surrogate marker for infectivity in peripheral tissues. Initial studies of post-mortem tonsil by Western blotting reported in 1999 have been extended to other post-mortem tissues of the lymphoreticular system, peripheral nervous tissue and other organ samples from cases of variant CJD and relevant controls. The results confirm: i) the presence of PrP^{res} in lymphoid tissue (tonsil, spleen and lymph node) in cases of vCJD, ii) the levels of PrP^{res} in vCJD lymphoid tissues are substantially lower than those found in the brain, iii) the absence of detectable PrP^{res} in lymphoid tissue from patients with sporadic CJD or iatrogenic CJD, iv) the presence of PrP^{res} in certain cranial nerves in cases of vCJD, sporadic CJD and iatrogenic CJD, and, v) the absence of detectable PrP^{res} in organs such as heart, lung and kidney in any form of CJD thus far examined. Since these conclusions are based on the somewhat limited sensitivity of Western blot analysis we are currently exploring the use of higher sensitivity assays for PrP, such as the DELFIA, and capillary electrophoresis assays.

Other activities

1. Retrospective analysis of PrP^{res} isotype in a series of fifteen cases of iatrogenic CJD (in progress).
2. Retrospective analysis of PrP^{res} isotype in a series of eight cases of CJD in individuals with mutations in the *PRNP* gene (in progress).
3. Participation in a National Institute for Biological Standards and Control (NIBSC) co-ordinated ring study to compare the sensitivity of PrP^{res} detection methods and to correlate this with CJD infectivity levels. A report will be issued by NIBSC in due course.
4. Investigation of Xenopus oocytes as a model system in which to express PrP^{C} (in collaboration with Dr John Connolly, Strathclyde University, funded by the MRC).
5. Analysis of PrP^{C} expression in the context of neurological disorders other than CJD (in collaboration with Professor Jeanne Bell and Dr Neil McLennan, University of Edinburgh).

4.4 Brain banking activities

The bank of fixed and frozen tissues in the Surveillance Unit was used extensively in 2000 for collaborative research purposes with colleagues in the UK and overseas. The reorganisation of specimens undertaken in the last year has now allowed more efficient storage of materials for research purposes.

4.5 Health and Safety

The Unit continues to work to the stated national guidelines and receives numerous requests for specialist advice in this field. No major problems were identified in the laboratory during the past year and there have been no difficulties associated with the transportation of diagnostic material to and from the laboratory.

SECTION

5

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SECTION

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