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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 encephalopathies (TSEs). In September 2001 the National Care Team was formed, which currently comprises a care coordinator and a secretary. The National Care Team is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

The information provided in this thirteenth report continues to provide evidence of a high level of case ascertainment. The decrease in referrals is however potentially concerning from the point of view of complete case ascertainment. The reason for this drop is unknown and the numbers will need careful monitoring over 2005. It is particularly notable that the number of recorded sporadic CJD deaths in 2004 is lower than in the three previous years, however, the death data for 2004 may be incomplete. Detailed clinical and epidemiological information has been obtained for the great majority of patients. The case-control study for risk factors of CJD has continued recruitment and initial analysis has been undertaken. The post mortem rate for patients with suspected CJD is high, although there is ongoing evidence that this rate continues to decline, in line with general autopsy rates in the UK. This is reflected in the reduced number of brain specimens examined in the neuropathology laboratory this year. The reduction in sporadic CJD numbers (32 in 2004, 52 in 2003) is another potential concern along with the fall in referral numbers and sporadic CJD deaths noted above.

In 1990-2004 mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.86, 1.05, 0.88 and 0.53/million/year. The difference between the rates in each country is not statistically significant ($p>0.2$). 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 ($p>0.2$). The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=135) and Northern Ireland (SMR=74).

Up to 31 December 2004, there have been 148 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 106 were confirmed by neuropathology. A further 5 probable cases were alive as at 31st December 2004. The clinical, neuropathological and epidemiological features of these cases of vCJD are remarkably uniform and consistent with our previous descriptions. Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2004 indicates that a peak has been passed. While this is an encouraging finding, incidence of vCJD may increase again, particularly if different genetic subgroups are found to be affected. The identification of disease-related PrP in the spleen of a blood recipient of PRNP-129 MVgenotype

emphasises this point. In addition, this case along with the report of the appendix study suggests at least a possibility of a greater number of preclinical or subclinical cases in the population than might be indicated by the present numbers of confirmed cases.

Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - all 131 cases (86%) of vCJD with available genetic analysis have been methionine homozygotes. The incidence of vCJD across the UK continues to show a "North-South" difference (though slightly less than previously reported), with a higher incidence being maintained in the North of the UK. The underlying reason for this finding is not clear. The only statistically significant geographic cluster of vCJD cases in the UK was in Leicestershire. All geographically associated cases of vCJD are considered for investigation according to a protocol which involves the NCJDSU, colleagues at the HPA, HPS and local public health physicians.

The activities of the NCJDSU are strengthened by collaboration in other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated; the effectiveness of this collaboration allowed the identification in 2003 of a case of variant CJD associated with blood transfusion and the identification in 2004 of PrP^{res} in the spleen of a blood recipient. The success of the National CJD Surveillance 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.

Section

2

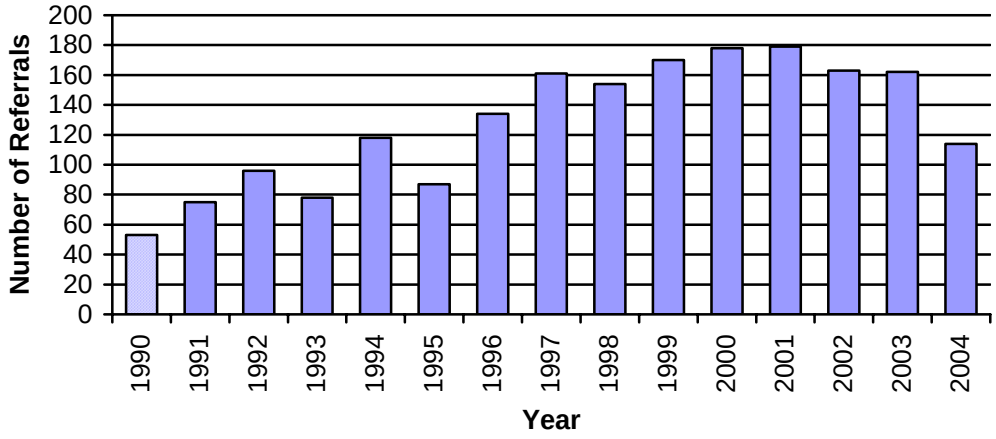
CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK 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 human infection with the agent responsible for the emergence of bovine spongiform encephalopathy (BSE) in cattle. Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD and variant CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings in relation to UK cases of sporadic, familial, iatrogenic and variant CJD referred up to 31st December 2004 (with data ascertained up to 14th February 2005). Data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective data are available from 1985.

2.1 Referrals to NCJDSU

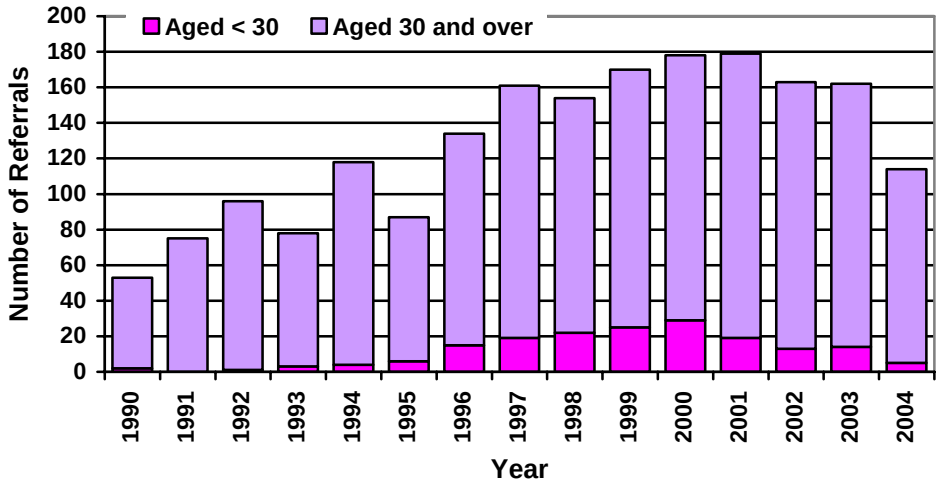
The NCJDSU receives referrals of suspect cases of CJD and a proportion of these will turn out not to have CJD. Referrals of suspect cases increased over the years after the present surveillance system began in 1990, particularly following the description of vCJD in 1996. Over the 1999-2003 period, the annual referral number varied only a little in the 162-179 range. In 2004, however, there were only 114 referrals, being the lowest level since 1996. The numbers are shown graphically in Figure 1a.

Figure 1a Referrals to NCJDSU : 1 May 1990 – 31st December 2004



When looking at the total number of referrals there is evidence of something changing during the period 2000-2004. The number of referrals aged less than 30 have been in decline since 2000, mirroring the decline in vCJD cases, and can probably be explained by the decline in vCJD cases over that period. The age group 30-59 show a fairly constant number of referrals over 2000-2003 with a large drop in 2004. It would be expected that this age range would include more sporadic cases and the observed pattern does not fit particularly with decline in vCJD cases. However, annual numbers of cases over the period 2000-2004 appear compatible with Poisson variation (test for extra Poisson variation $p>0.5$); i.e. pattern compatible with random variation. The age group 60 and over show a similar pattern to the 30-59 age group with a fairly constant rate of referrals over 2000-2003 and a large drop in 2004. The annual number of cases over the period 2000-2004 appear compatible with Poisson variation (test for extra Poisson variation $p=0.34$); i.e. pattern compatible with random variation. Looking at all referrals during 2000-2004, if the youngest age groups (< 30) are excluded, there is only weak evidence that something has changed ($p=0.07$). Figure 1b shows numbers of referrals to NCJDSU split between age groups <30 and ≥ 30.

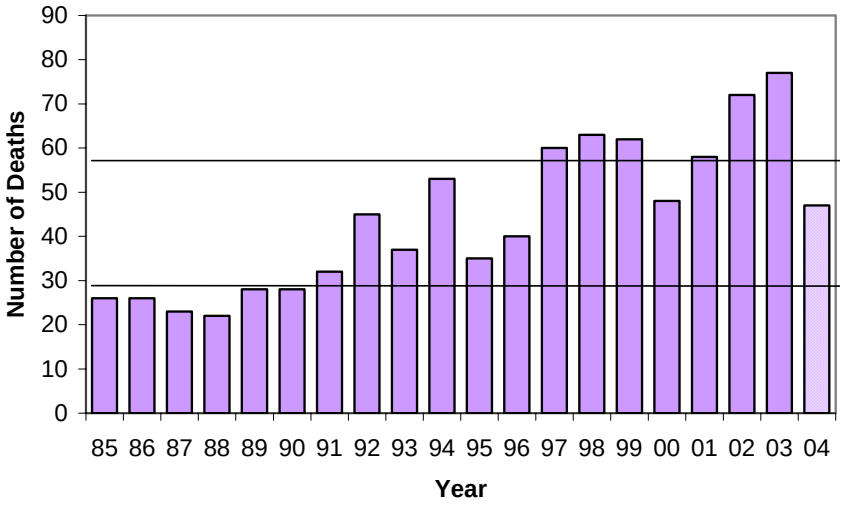
Figure 1b Referrals to NCJDSU : 1 May 1990 – 31st December 2004 Age < 30 and Age ≥ 30



2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2004, 1164 cases of sporadic CJD were identified in the UK, of which 14 cases were still alive on 31st December 2004. Two further cases were identified in Jersey but they were not included in the following UK analyses. Of these UK cases, 881 (76%) were classified as definite cases with the remainder classed as probable. Figure 2a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2004, Figure 2b shows similar data for England and Wales between 1970 and 2004 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2004. In England and Wales the number of deaths identified each year 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. Over the period 1990-2004 the average crude annual mortality rates from sporadic CJD per million population were 0.86 in England, 1.05 in Wales, 0.88 in Scotland and 0.53 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 ($p > 0.2$).

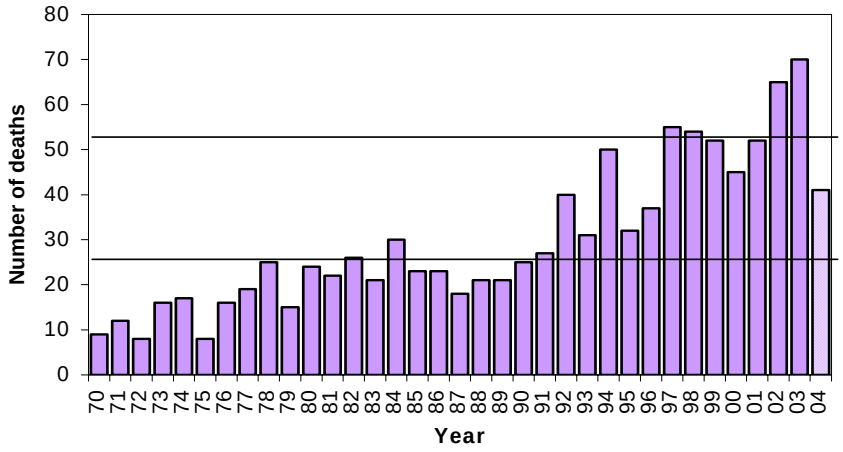
Figure 2a Deaths from sporadic CJD, UK, 1985-2004



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

Data for 2004 may be incomplete

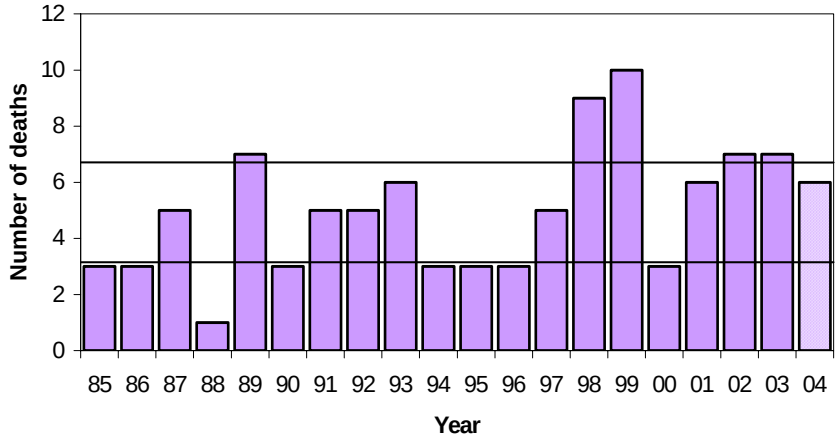
Figure 2b Deaths from sporadic CJD, England and Wales, 1970-2004



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

Data for 2004 may be incomplete

Figure 2c Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2004 (please note different scale from Figs 1a and 1b)



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

Data for 2004 may be incomplete

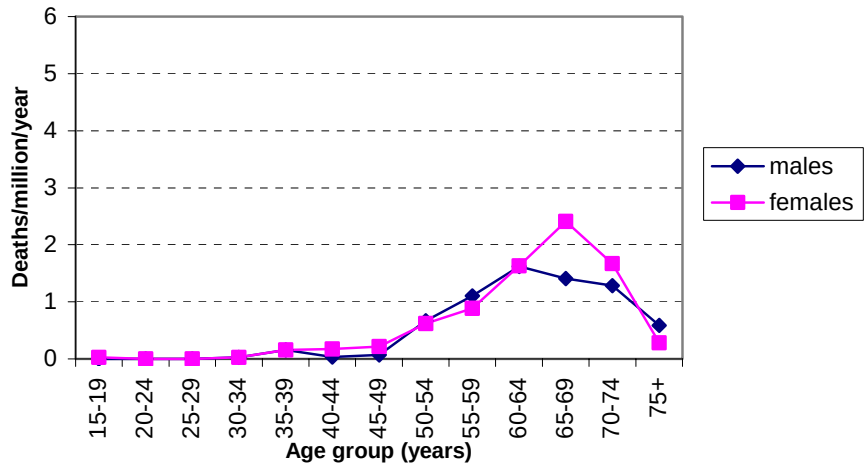
Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1st January 1990 to 31st December 2004

	No of cases	Total no (mortality rate/million/ annum)*		No of cases	Total no (mortality rate/million/ annum)*
ENGLAND			**ENGLAND**		
North			Yorkshire & Humberside		
Cleveland	6		Humberside	8	
Cumbria	9		NorthYorkshire	12	
Durham	6	39 (0.84)	South Yorkshire	22	66 (0.88)
Northumberland	4		West Yorkshire	24	
Tyne & Wear	14				
			East Anglia		
East Midlands			Cambridgeshire	6	
Derbyshire	9		Norfolk	13	32 (1.01)
Leicestershire	13		Suffolk	13	
Lincolnshire	9	46 (0.75)			
Northamptonshire	2		South West		
Nottinghamshire	13		Avon	17	
			Cornwall	12	
South East			Devon	16	
Bedfordshire	6		Dorset	17	92 (1.28)
Berkshire	10		Gloucestershire	10	
Buckinghamshire	5		Somerset	10	
East Sussex	9		Wiltshire	10	
Essex	27				
Greater London	71	214 (0.80)	West Midlands		
Hampshire	22		Hereford & Worcs.	8	
Hertfordshire	11		Shropshire	4	
Isle of Wight	2		Staffordshire	17	61 (0.77)
Kent	17		Warwickshire	3	
Oxfordshire	9		West Mids (Met)	29	
Surrey	7				
West Sussex	18				
North West					
Cheshire	12				
Greater Manchester	26	80 (0.83)	**TOTAL FOR ENGLAND**		**630 (0.86)**
Lancashire	20				
Merseyside	22				
WALES			**SCOTLAND**		
Clwyd	7		Borders	3	
Dyfed	3		Central	5	
Gwent	7		Dumfries & Galloway	0	
Gwynedd	10		Fife	2	
Mid Glamorgan	11		Grampian	11	
Powys	2		Highland	1	
South Glamorgan	3		Lothian	17	
West Glamorgan	3		Strathclyde	25	
			Tayside	2	
TOTAL FOR WALES		**46 (1.05)**	Islands (Shetland)	2	
			Islands (Orkney)	0	
NORTHERN IRELAND	13	**13 (0.53)**	Islands (Western Isles)	0	
			TOTAL FOR SCOTLAND		**68 (0.88)**

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 15-year period of the study.

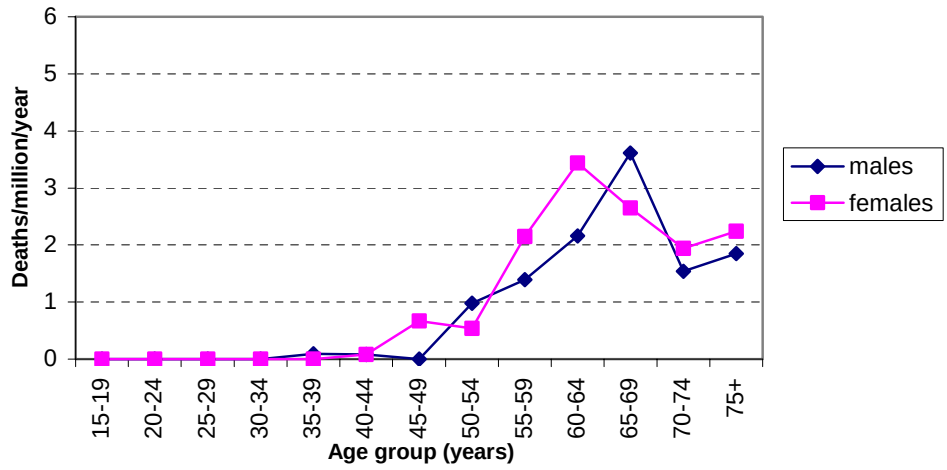
Figure 3a, 3b and 3c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-04, respectively. The median ages of cases at death during these time periods were 64, 66 and 67 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased until the ages of 60-69 years and then declined. The decline in mortality rate in the older age groups was more marked prior to 1990. The mortality rate in those aged 75 years and above was 2.83 cases/million/year in 1996-04, 2.11 cases/million/year in 1990-95 and 0.38 cases/million/year in 1970-89. This might be explained by an increase in case ascertainment in the elderly over time. Another feature over the time period studied, a change in the sex ratio, affecting particularly older cases, with a male excess after 1996, was examined in the 2001 annual report. The explanation for this trend remains unclear.

Figure 3a Age- and sex-specific mortality rates from sporadic CJD in the UK 1970-1989 (note: from 1970-1984 only England & Wales, thereafter UK)



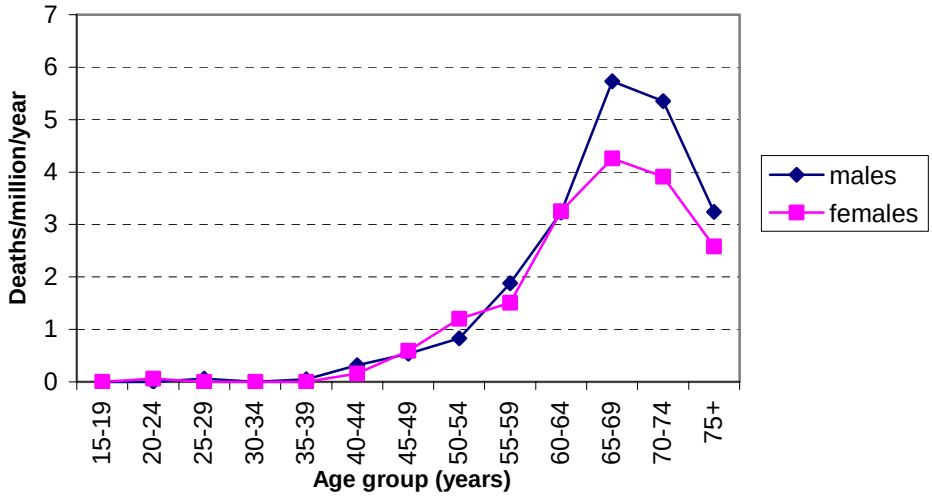
Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

Figure 3b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1995



Mortality rates calculated using 1991 Census

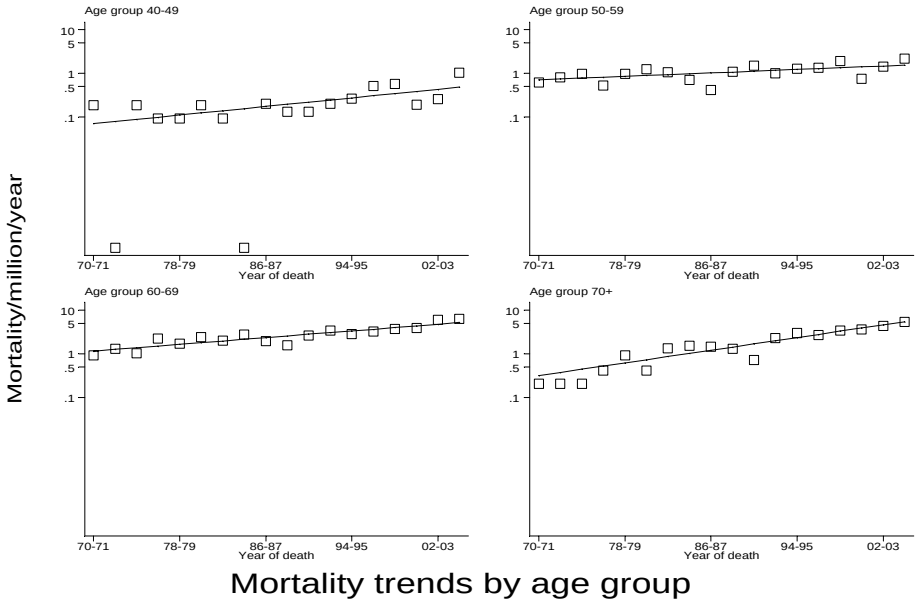
Figure 3c Age- and sex-specific mortality rates from sporadic CJD in the UK 1996-2004



Mortality rates calculated using 2001 Census

An analysis of age specific trends from 1970 to 2004 (Figure 4) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase 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 in all age groups ($p=0.001$, $p=0.001$, $p<0.001$, $p<0.001$ for age groups 40-49, 50-59, 60-69 and ≥70 years respectively). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

Figure 4 Trends in mortality from sporadic CJD by age: 1970-2004



Mortality rates calculated using 1981, 1991 & 2001 Census for time periods 1970-1985, 1986-1995 and 1996-2004 respectively.

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 <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 25 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 (yrs)	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	00-01	02-03	04[2]	**Total[2,3]**
10-19	0	0	0	0	0	1	0	0	0	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	0	0 (0)	**2 (0)**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1	0	0	0 (0)	**14 (0)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	9	3	4	4 (0)	**51 (0)**
50-59	7	9	11	6	11	14	12	8	5	13	18	12	15	20	28	11	21	8 (5)	**229 (5)**
60-69	9	13	10	22	17	24	20	28	22	18	30	39	32	35	40	43	65	17 (6)	**484 (6)**
70-79	2	2	2	4	9	4	11	16	18	14	7	21	34	30	35	38	49	12 (2)	**308 (2)**
80-89	0	0	0	0	0	0	2	0	0	2	2	7	3	6	10	11	9	6 (1)	**58 (1)**
90+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0 (0)	**2 (0)**
Total	**21**	**24**	**25**	**35**	**40**	**46**	**47**	**56**	**49**	**50[3]**	**60**	**82**	**88**	**100**	**125**	**106**	**149**	**47 (14)**	**1150 (14)**

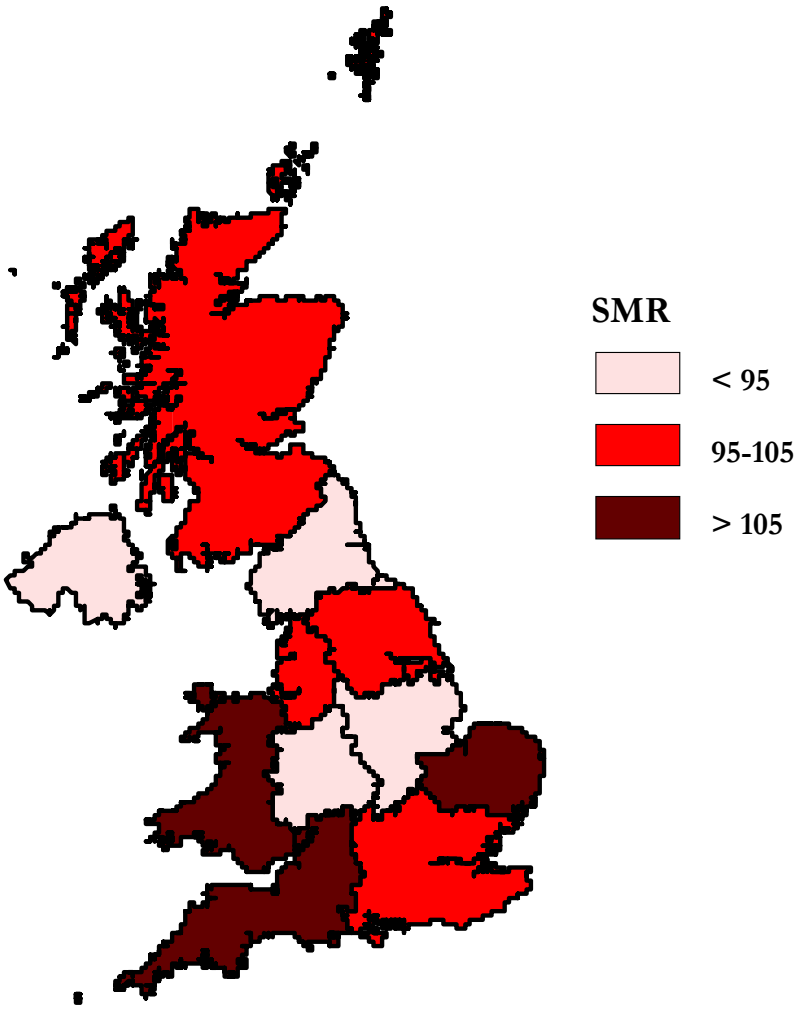
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

[2] Deaths up to 31st December 2004. Numbers in parentheses indicate additional cases alive on 31st December 2004. Data for 2004 not yet complete.

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

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2004 were calculated (Figure 5). After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p>0.2$). An SMR of 100 equates to average mortality rate. Regions of relatively high mortality are South West (SMR=135), East Anglia (SMR=114) and Wales (SMR=112). Low mortality rates were observed in Northern Ireland (SMR=74), West Midlands (SMR=86) and East Midlands (SMR=88). The highest SMR (135 in South West) arose from 91 cases observed compared with 68 expected, an excess of about 1.5 cases every year compared to the national average. In East Anglia and Wales the total numbers of excess cases were approximately 4 and 5 respectively.

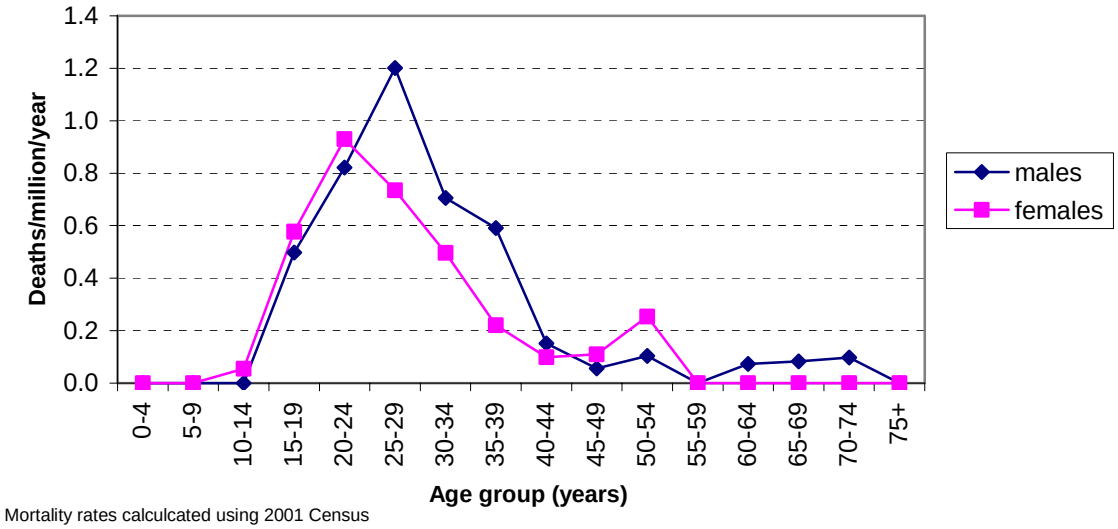
Figure 5 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2004



2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2004, 153 cases of definite or probable vCJD had been identified in the UK (106 definite, 41 probable who did not undergo post mortem, one probable awaiting post mortem confirmation and 5 probable cases still alive). Sixty-seven (44%) of the 153 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 66 years for the median age at onset and 67 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. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2004 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-39). The median duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2004.

Figure 6 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2004



Mortality rates calculcated using 2001 Census

Incidence of vCJD onsets and deaths from January 1994 - December 2004

Each quarter data on diagnosed cases of variant Creutzfeldt-Jakob disease (vCJD) in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The following analysis reviews the data to the end of December 2004 by which time there was a total of 153 cases of which 148 had died.

Methods

Onsets:

The incidence of onsets by quarter was analysed with Poisson models using polynomials (constant, exponential, quadratic exponential, cubic exponential). When modelling the incidence of onsets over time, delay to diagnosis, and the fact that this delay may be shortening over time because of new diagnostic methods, must be taken into account. Consequently the data were cross-classified by quarter of onset and number of quarters delay from onset to diagnosis, and the delay from onset to diagnosis modelled using a gamma distribution with a mean that can vary over time. A further model looking at a rise to a plateau is also fitted to see if there is evidence that the epidemic has reached a constant level (at least temporarily).

Deaths:

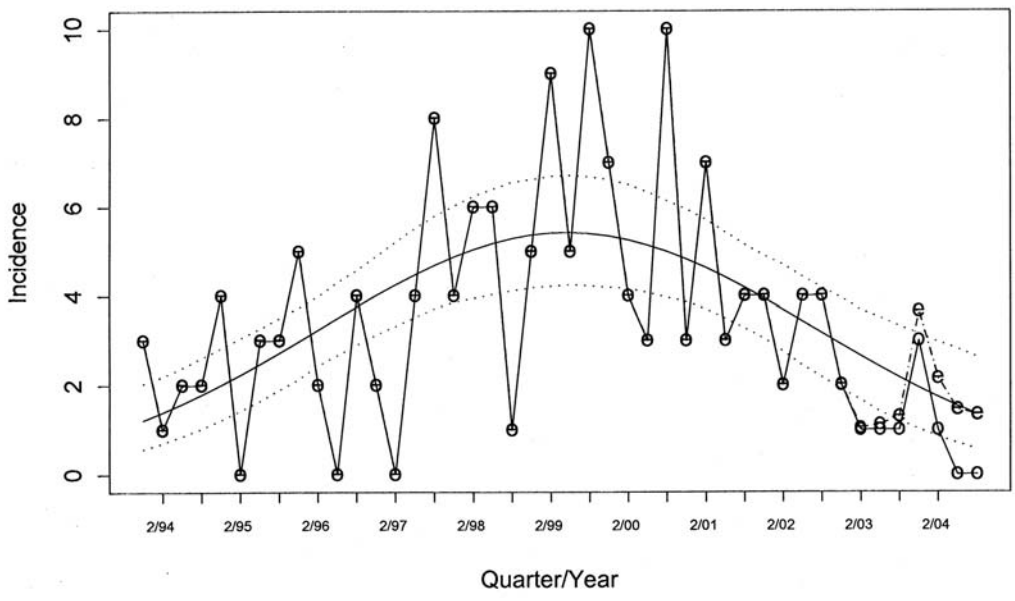
After grouping deaths by quarter the incidence of deaths were modelled by Poisson regression using polynomials. Most deaths are reported quickly so an adjustment for reporting delay is not necessary. So far the age at death has not increased as might have been expected, assuming that most exposure to BSE ceased in the early 1990s. In order to examine this further the cases were stratified by quarter of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts. A further model looking at a rise to a plateau is also fitted.

Results for Onsets

Since vCJD was first identified, the average interval between the onset of first symptoms and the diagnosis of vCJD has decreased. The mean delay to diagnosis is estimated to have reduced by an average of 4% per year and is currently estimated at 9 months.

The model providing the best fit to the data is shown in Figure 7. This model has a quadratic trend and fits the data better than a simple exponential trend ($p<0.001$). The quadratic model is consistent with an epidemic that has reached a peak and this model gives an estimated current incidence of 1.2 onsets per quarter. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in mid 1999. A model was also fitted with an increase to a plateau, but this model did not fit the data as well as the quadratic model (deviance greater by 22 on the same number of parameters), providing evidence that a peak has been passed.

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



Predicted onsets by the end of December 2004

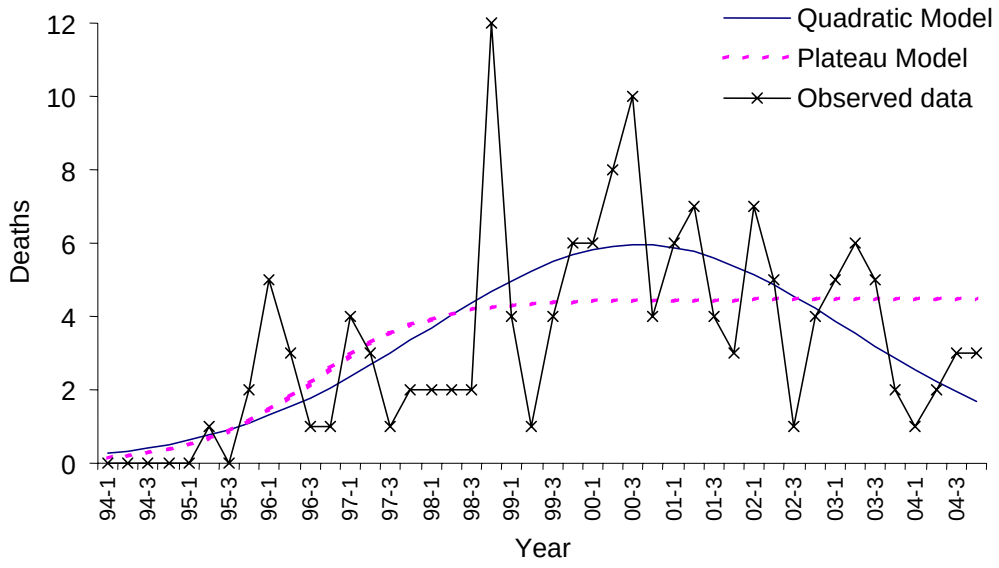
Based on the quadratic model, the estimated total number of cases with onset by December 2004 is 158 (153 already diagnosed + 5 not yet diagnosed) with a 95% prediction interval of 155 to 163.

Results for Deaths

All deaths combined

As with onsets, the quadratic trend model provided the best fit with a significant improvement on the simple exponential model ($p<0.001$). This model is shown in Figure 8 and estimates that the current quarterly incidence of deaths is 1.7. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in mid 2000. The model with a rise to a plateau gave significant evidence of a lack of fit ($p=0.02$), again indicating that a peak has been passed. A model with a cubic term was also fitted by did not provide an improved fit ($p=0.14$).

Figure 8 Quadratic and plateau models for vCJD deaths incidence trend



Predictions for deaths in 2005

The model with the quadratic term predicts a total of 6 deaths in 2005 with a 95% prediction interval of 2 to 13. It is not sensible to predict deaths based on the other models.

Assessment of Predictions made at the end of December 2003

The exponential model predicted 27 deaths for 2003 with a 95% prediction interval of 16-39; the quadratic model predicted 11 deaths for 2003 with a 95% prediction interval of 4-19 and the plateau model predicted 19 deaths for 2003 with a 95% prediction interval of 10-29.

The actual observed number was 9 which is consistent with the quadratic model but not the exponential or plateau models.

Deaths by cohort

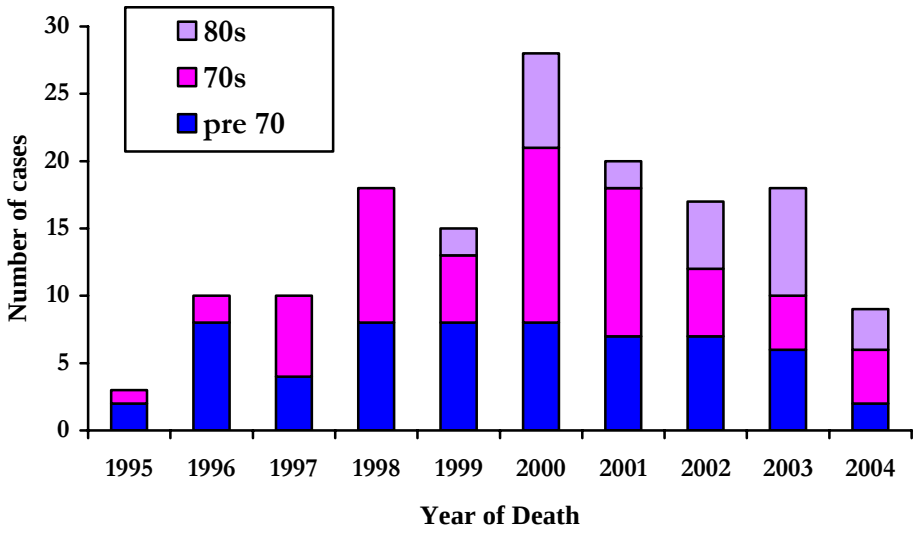
The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. This finding is consistent with a number of possible explanations, for example:

- varying age-specific susceptibility (teenagers and young adults are maybe inherently more susceptible to infection).

- age-specific exposure (possible different dietary habits in teenagers and young adults).
- different incubation periods by age (teenagers and young adults might have shorter incubation periods).

To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves ($p<0.001$). The main difference is the absence of deaths in the 1980s cohort prior to 1999 (Figure 9). In all three birth cohorts the quadratic model provides an improved fit compared to an exponential increase model ($p<0.02$).

Figure 9 Deaths by year and birth cohort



Summary

There is strong evidence ($p<0.001$) that the epidemic is no longer increasing exponentially. Estimates from quadratic models suggest that the epidemic may have reached a peak in mid 1999 for onsets or mid 2000 for deaths. An alternative model with an increase to a plateau rather than a peak does not fit the data well, indicating that a peak has been passed.

For the purposes of short-term predictions, the model used is important; predictions are best made based on the quadratic model rather than the plateau or exponential model. The quadratic models estimate the current incidence of onsets to be 1.2 per quarter and deaths to be 1.7 per quarter with 6 deaths predicted in the next 12 months (95% prediction interval 2 to 13).

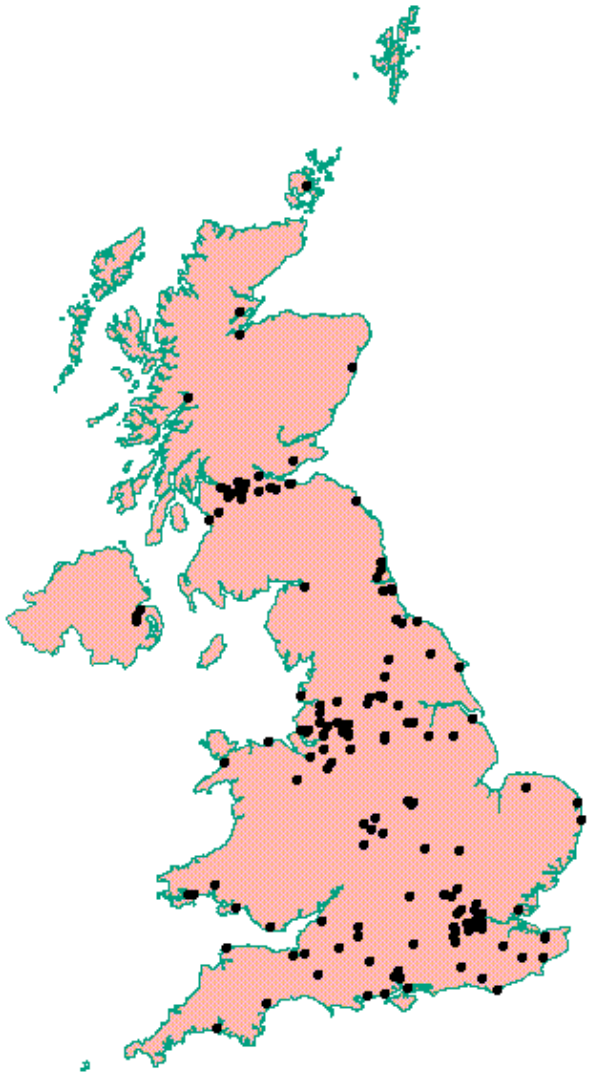
An analysis that looked at deaths by birth cohort (pre 1970, 1970s, 1980s) showed that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s were only seen from 1999 onwards.

Although the best fitting model indicates that a peak has been passed, this does not exclude the possibility of future peaks. There is the possibility of epidemics in other genetic sub-populations and also human-to-human spread.

Geographical distribution of variant CJD

Figure 10 shows the geographical distribution, by place of residence at onset, of 152 cases of vCJD in the UK for whom a residential address at onset is available. For one case the address at onset is known only at county level. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution, by county of residence at onset, of the cases who had died by 31st December 2004 (for whom information on place of residence at onset was available) along with the crude mortality rate per million population per annum of each standard region.

Figure 10 Geographical distribution of places of residence at onset of symptoms of vCJD (n=152*)



* in one case only county of residence was known and could not be plotted.

Table 3 Cases of definite and probable vCJD shown by region and county of onset (n=153†) and region and county of death (n=145‡)

	No of cases resident at onset	No of cases resident at death (mortality rate*)
ENGLAND		
North		
Cleveland	3	3
Cumbria	1	1
Durham	1	2
Northumberland	3	4
Tyne & Wear	4	2
Total	**12**	**12 (0.40)**
East Midlands		
Derbyshire	0	1
Leicestershire	4	5
Lincolnshire	2	2
Northamptonshire	1	1
Nottinghamshire	0	0
Total	**7**	**9 (0.23)**
South East		
Bedfordshire	0	0
Berkshire	0	1
Buckinghamshire	0	0
East Sussex	2	2
Essex	1	0
Greater London	16	14
Hampshire	6	3
Hertfordshire	3	3
Isle of Wight	0	1
Kent	5	5
Oxfordshire	1	1
Surrey	5	3
West Sussex	1	1
Total	**40**	**34 (0.20)**
North West		
Cheshire	7	8
Greater Manchester	9	8
Lancashire	4	4
Merseyside	3	3
Total	**23**	**23 (0.37)**
WALES		
Clwyd	1	0
Dyfed	3	3
Gwent	0	0
Gwynedd	1	1
Mid Glamorgan	0	0
Powys	0	0
South Glamorgan	1	1
West Glamorgan	1	0
WALES TOTAL	**7**	**5 (0.18)**
NORTHERN IRELAND TOTAL	**3**	**2 (0.13)**

	No of cases resident at onset	No of cases resident at death (mortality rate*)
ENGLAND		
Yorkshire & Humbs		
Humberside	2	2
NorthYorkshire	3	2
South Yorkshire	4	4
West Yorkshire	6	7
Total	**15**	**15 (0.31)**
East Anglia		
Cambridgeshire	1	1
Norfolk	2	2
Suffolk	1	1
Total	**4**	**4 (0.20)**
South West		
Avon	1	0
Cornwall	2	1
Devon	2	3
Dorset	1	1
Gloucestershire	0	0
Somerset	4	5
Wiltshire	3	1
Total	**13**	**11 (0.24)**
West Midlands		
Hereford & Worcs.	0	1
Shropshire	1	1
Staffordshire	0	0
Warwickshire	1	2
West Mids (Met)	4	5
Total	**6**	**9 (0.18)**
ENGLAND TOTAL	**120**	**117 (0.25)**
SCOTLAND		
Borders	0	0
Central	1	1
Dumfries & Galloway	0	0
Fife	1	1
Grampian	1	1
Highland	3	2
Lothian	4	4
Strathclyde	12	12
Tayside	0	0
Islands (Shetland)	0	0
Islands (Orkney)	1	0
Islands (Western Isles)	0	0
SCOTLAND TOTAL	**23**	**21 (0.42)**

* mortality rate/million/annum based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the period 1st May 1995 to 31st December 2004.

† includes cases still alive at 31st December 2004.

‡ excludes 3 cases who died abroad.

Table 4 shows cumulative regional rates of vCJD based on cases' place of residence in 1991, rather than at onset, and the population aged 10 years and above resident at that time. We originally 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.

Age- and sex- standardised "incidence" ratios (SIRs) based on cases' place of residence in 1991 are shown in Figure 11 for the 11 standard regions of the UK.

Table 4 Distribution of 153 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	18 (4.12)
North	2,635,785	11 (4.17)
Yorkshire & Humberside	4,202,051	15 (3.57)
North-West	5,326,333	23 (4.32)
East Midlands	3,444,391	12 (3.48)
West Midlands	4,464,592	10 (2.24)
East Anglia	1,775,687	5 (2.82)
Wales	2,466,669	5 (2.03)
South-East	15,010,650	40 (2.66)
South-West	4,055,268	11 (2.71)
Northern Ireland	1,320,430	3 (2.27)
Total	49,065,540	153 (3.12)

Figure 11 **Standardised incidence ratios (SIRs) up to 31st December 2004 of vCJD by standard region on 1st January 1991**

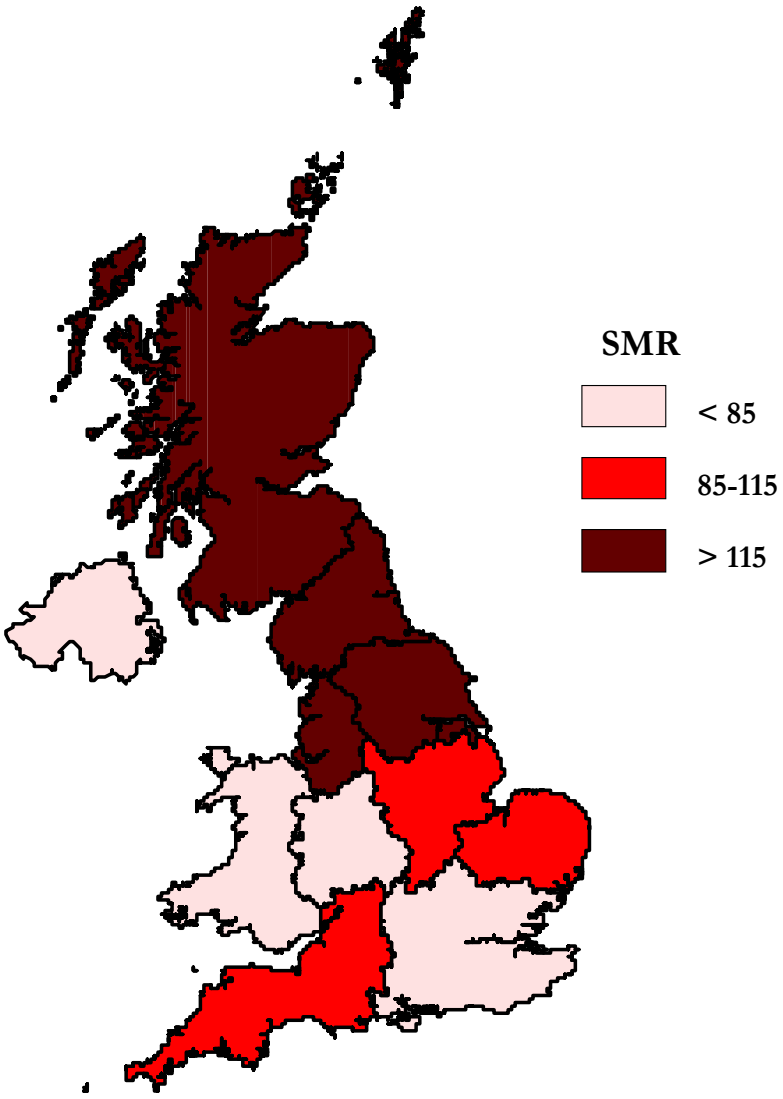


Table 5 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991, for those cases included in the initial analysis in the 1999 Annual Report (n=51) and for all cases. The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has been largely maintained as further cases with, overall, a rate ratio controlling for age and sex of 1.53 (95% c.i., 1.11, 2.11), i.e. individuals living in the "North" in 1991 are about one and a half times more likely to have developed vCJD than individuals who were living in the "South" in 1991. The overall rate ratio has been slightly reducing each year since first reported.

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	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	67 (4.05)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	83 (2.66)
Total (rate ratio*)	47.8 million	51 (1.94)	150 (1.53)

*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 27 years versus 25 years; p=0.7), a similar proportion were male (54% versus 57% of southern cases; p=0.7).

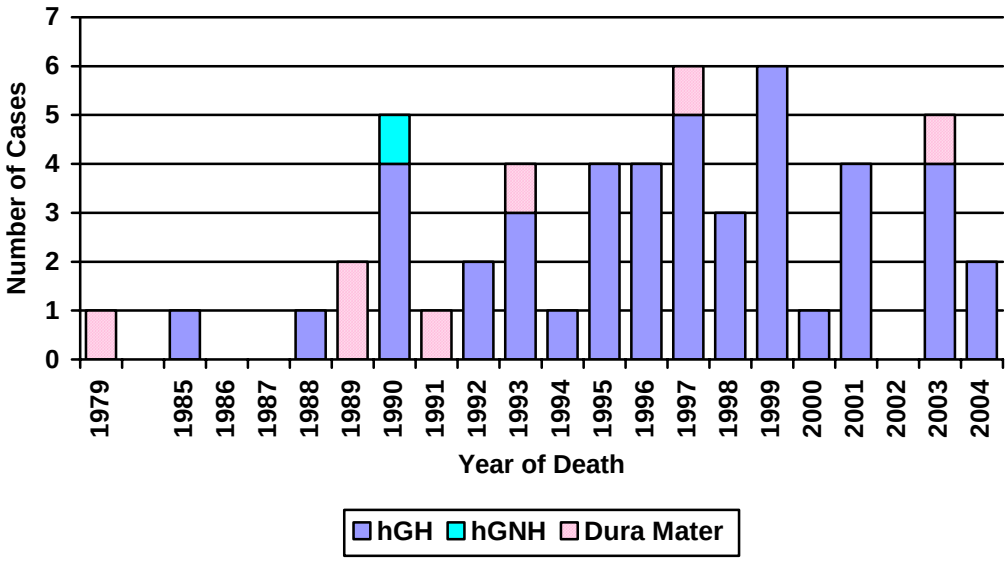
Geographically Associated Cases of variant CJD

Geographically associated cases of variant CJD are defined by two or more cases of probable or definite vCJD with a geographical association, either through proximity of residence or through another link with the same location (occupational, educational or social/recreational). By the end of December 2004 a total of thirteen investigations into geographically associated cases of vCJD had been opened in the UK. Those in eleven localities were concluded and in two were ongoing. The Leicestershire cluster of five cases remains the only statistically significant cluster of cases of vCJD in the UK to date. None of the concluded investigations have revealed any suggestion of possible iatrogenic transmission. No evidence emerged from these investigations in any of the areas apart from Leicestershire of bovine heads being split or brains removed by local butchers in their shops during the relevant time period.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2004, 57 cases of CJD attributable to iatrogenic exposure have been identified, 7 in individuals receiving dura mater implants, 49 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Fifty-three of these individuals have died (Figure 12) and 4 were still alive as at 31st December 2004.

Figure 12 Deaths from iatrogenic CJD, 1979-2004



The mean age at death of the hGH/hGN group was 31 years (with a range of 20-46 years) and for the dura mater cases 42 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. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations.

2.5 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 all identified 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

The following results are based on vCJD cases who donated or received blood and does not include data on the ongoing study of sporadic CJD.

Twenty-eight vCJD cases were reported to have been blood donors. Two additional cases who were not reported to have been blood donors were found to be registered with UKBTS. One of these cases was found to have been a blood donor while the other case was registered as a donor but never made any donations. Twenty cases have been traced at blood centres, including the two additional cases mentioned above. Components derived from donations made by 16 of these individuals were actually issued to hospitals. It has been established that 50 components were transfused to named recipients. One of these recipients was identified as developing symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor developed symptoms of vCJD[1]. In a further recipient who died from a non-neurological disorder 5 years after receiving blood from a donor who subsequently developed vCJD, protease-resistant prion protein (PrP^{res}) was detected in the spleen but not in the brain. This is the first recorded case in the UK of autopsy detection of presumed preclinical or subclinical vCJD infection[2].

In the reverse study, 9 vCJD cases were reported to have received blood transfusions in the past. A further case received a blood transfusion after onset of illness. Checks revealed that 2 of these cases were not transfused, 2 had transfusions which predated available records and 6 had records of transfusion which could be traced. These 6 individuals had received 125 components of blood (with one patient given 103 components), which have been traced to 123 named donors (one of whom had vCJD as described above). The donors of two components are not traceable.

Conclusion

These findings raise the possibility of a transfusion transmitted case of vCJD. Infection in the recipient could have been due to past dietary exposure to the BSE agent. However, the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15 000 to 1 in 30 000.[1]

(Collaborators on this project: Dr P.E. Hewitt, Dr C.A. Llewelyn, Ms M Malfroy).

[1] Llewelyn CA, Hewitt PE, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; 363: 417-421.

[2] Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient. Lancet 2004; 364: 527-529.

2.6 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[3,4].

After almost 8 years surveillance, 1866 patients with suspected PIND have been reported. The Expert Group has discussed 1326 cases, of which 773 have a confirmed underlying cause other than vCJD, being categorised into 114 known neurodegenerative diseases. Among them were six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

(Collaborators: Dr C. Verity, Dr A. Nicoll, Ms L. Stellitano, Ms AM Winstone)

[3] 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.

[4] Devereux G, Stellitano L, Verity CM et al. Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). Arch Dis Child 2004;89:8-12.

Section

3

CASE-CONTROL STUDY

Since May 1990 a case-control study of CJD has been carried out in the UK to investigate potential risk factors for variant and sporadic CJD. Patients themselves are usually too unwell to answer questions when they are seen by members of the Unit. Therefore, relatives of patients with suspected CJD are approached and, with informed consent, interviewed using a standard questionnaire relating to possible risk factors for CJD, including residential, occupational, dietary and medical histories. To maximise the study's validity, it is important that this interview takes place as early as possible, that is, as soon as a person is suspected as having CJD. We are indebted to the families of those with suspected CJD, who agree to be interviewed at what is an extremely difficult time in their lives.

The choice of the source of controls is extremely important in a case-control study. There are a number of possible choices each of which has its own advantages and disadvantages in terms of suitability as controls, practicalities of recruitment and cost. Since 1990 there have been some variations in control recruitment for the CJD risk factor study:

1990-1997: For each suspect case, an age- and sex-matched patient at the same hospital was identified as a control.

1998-2002: With the diagnosis of the first cases of variant CJD, it was decided that in addition to hospital controls for variant cases, and instead of hospital controls for sporadic cases, community controls would be recruited, matched for sex and age, through general medical practices (one control for each sporadic case and up to 4 controls for each variant case). Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. However, major difficulties were encountered arising from the complex process of recruitment of general practice based controls. Of particular concern was the low response rate to the initial letter from the GP to the potential control. With a low response rate, the results from the study would be hard to interpret because of the potential for selection bias. Therefore, a revised strategy for control recruitment was devised and recruitment of this group of controls ceased.

2002 to date:

Hospital controls continue to be recruited for variant cases where possible. Seventy-seven hospital controls have been recruited for variant cases to date.

During 2002/03 a one-off recruitment of approximately 900 general population controls was carried out on our behalf by the National Centre for Social Research, which is the largest independent social research institute in Britain. (Detailed information on how these controls were recruited by the National Centre for Social Research was shown in last year's report).

These controls represent a wide age range so that their data can be compared with that from both variant and sporadic cases.

In 2004, we carried out the first analysis of data from variant cases compared with these general population controls. This analysis has been written up and submitted for publication. Later in 2005, we shall begin analyses to compare sporadic cases with this group of controls.

In addition to the data we have acquired from relatives of cases and controls, we also seek medical and surgical data from medical records. In light of the probable secondary transmission of vCJD by blood transfusion, it is especially important to investigate medical/ surgical risk factors for CJD. The data acquired from primary care records is likely to be more accurate and detailed than that obtained from relatives. For the cases this is done prospectively as they are identified. We also have written consent from three-quarters (approximately 600) of those general population controls, who were asked, to access their primary care medical and dental records. To actually collect this information is a huge task and involves visiting practices throughout the whole of the UK. This work is in progress for primary care medical records and we are about to embark on a pilot project with colleagues at Glasgow Dental School to investigate whether it is possible and feasible to trace dental records.

We are currently recruiting a second group of controls comprising friends nominated by relatives of cases. That is, relatives of cases are asked to nominate a friend who would agree to be interviewed about a relative of theirs (the control), who is age- and sex-matched to the case. The degree of relative between control and 'friend' is matched to that between the case and their relative. Consent of the control is sought before the 'friend' is interviewed.

This is a complex, ongoing process, involving relatives of cases at a difficult point in their lives. Therefore, often relatives need time (sometimes many months, especially if their relative has recently died) to consider whether they wish to take part in the study and, of course, they can change their mind at any time in the process. Once they have agreed to take part they then need to be able to identify a suitable friend. The friend then needs to be contacted by one of the Unit's research nurses and agree to take part in the study. If they do agree to take part, a suitable relative of the 'nominated' friend needs to be identified, contacted and agree to participate. Finally if both 'nominated' friend and their relative have agreed to take part in the study, the interview can take place between the friend and one of the Unit's research nurses.

Table 6 summarises, to April 2005, the progress made in recruiting relative-nominated controls. The table shows that control recruitment has been completed for a third each of variant (11/34) and sporadic (67/201) cases approached. Looking in more detail, relatives of 68% (23) of variant cases and 71% (143) of sporadic cases agreed to participate in the study. However, of those agreeing, 8 (35%) of the relatives of variant cases and 36 (25%) of the relatives of sporadic cases were unable to nominate a friend. This was because either they had not told a suitable friend about the illness or they did not have a friend with a suitable relative. Of those cases for whom control recruitment is ongoing, relatives of 4 variant cases and of 14 sporadic cases are currently undecided as to whether to participate in the study. Relatives of 19 sporadic cases have agreed to participate in the study and are in the process of identifying a friend with a suitable relative whom they can nominate.

Table 6: Relative nominated controls - recruitment process

	Variant CJD Number	**Sporadic CJD** Number
Relatives of cases approached	34	201
▪ Relatives of cases agreeing to participate and able to nominate a friend	15	107
▪ Relatives agreeing to participate but unable to nominate a friend	8	36
▪ Relatives considering whether to participate	4	14
▪ Relatives of cases refused	7	44
Friend of relative contacted	14	88
Friend of relative agreeing to participate	12	75
Control consented	11	75
Control interviewed	11	67

Section

4

LABORATORY ACTIVITIES

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis and PrP genetic studies) and post-mortem (neuropathology and protein studies). The NCJDSU has facilities to perform all of these investigations, which aid the timely and accurate diagnosis of all forms of CJD and are essential for surveillance purposes.

4.1 Neuropathology – Statement of Progress

The neuropathology laboratory in the NCJDSU continues to maintain its diagnostic and research activities, including the work of the protein laboratory. The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory continues its major role in the National Retrospective Review of CJD and Related Disorders and in the retrospective study to detect abnormal PrP in anonymised specimens of appendix and tonsil tissue. Since 2001 the autopsy rates for sporadic and variant CJD have declined, in keeping with national trends. This is reflected in the number of cases examined in 2004, with a decline in the cases for both sporadic and variant CJD, and a marked variability in case referral rates. As a result of the Department of Health's guidelines for the examination of brain biopsy specimens, the number of cerebral biopsies referred to NCJDSU has increased. These samples require intensive investigation by conventional histology, immunocytochemistry, PET blot and western blot analysis. Many of these biopsy samples do not show any specific histological abnormalities, and so a conclusive diagnosis cannot always be reached, although a descriptive report is issued for each case. Most of these cases show negative findings for CJD in terms of the investigative parameters mentioned above. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all 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 2004

A detailed breakdown of laboratory activities is summarised in Table 7. These demonstrate that the total number of cases referred to the laboratory from the UK has declined in comparison with the previous year, involving both sporadic and variant CJD cases. Neuropathological referrals are made from pathologists across the UK and overseas. These include cases where a preliminary histological diagnosis of CJD has been made, cases which have undergone autopsy but no histological examination has been undertaken in a patient with suspected CJD, and cases where a diagnosis of CJD is thought unlikely, but no specific histological diagnosis has been made. The latter are usually referred to help the exclusion of

CJD from the differential diagnosis. Material from DH-funded research projects is also referred to the NCJDSU, particularly in the UK Haemophilia Study (Director: Professor Christine Lee, Royal Free Hospital, London). In contrast to last year, the most frequent alternative diagnoses for sporadic CJD is dementia with Alzheimer's disease. The pathological features of variant CJD cases have again been reviewed (see publications list). This has indicated that the pathological phenotype of variant CJD has remained relatively constant over the past 9 years, in terms of the changes occurring in the central nervous system and in peripheral tissues, particularly lymphoid tissues. One of the cases examined in 2004 was a unique example of probable iatrogenic transmission of vCJD infectivity following blood transfusion in a *PRNP* codon 129 heterozygote who died of unrelated causes to CJD and had developed no clinical symptoms of a neurological disorder. Western blot and immunocytochemical studies showed disease-associated PrP in the spleen and cervical lymph nodes, but not in the brain or spinal cord.

The laboratory is a major contributor to the World Health Organisation TSE Diagnostics Working Group, and continues to act as an international reference centre for the diagnosis of CJD.

Table 7 Breakdown of Laboratory Activities 1st January 2004 – 31st December 2004

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	32	52
Familial CJD	0	2
Variant CJD	3	10
Iatrogenic CJD (growth hormone therapy)	2	3
Iatrogenic CJD (Lyodura)	1	0
Gerstmann-Straussler-Scheinker syndrome (GSS)	0	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative diagnosis)*	22	17
Alzheimer's disease	8	2
Dementia with Lewy Bodies	0	3
Other forms of brain disease†	3	3
REFERRED CASES (EUROPEAN UNION)		
Sporadic CJD	1	5
Familial CJD	0	1
Variant CJD	1	0
GSS	0	0
Other forms of brain disease	1	8
REFERRED CASES (REST OF WORLD)		
Sporadic CJD	0	4
Variant CJD	2	0
Familial CJD	1	0
Other forms of brain disease	2	6
TOTAL NUMBER OF CASES	**79**	**116**

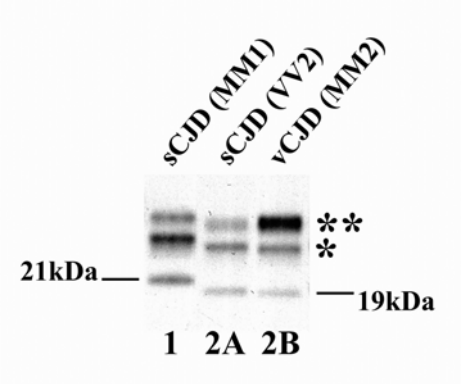
* Cases with no specific histological or biochemical evidence of CJD, in whom no specific alternative diagnosis can be made. These cases are usually submitted for the exclusion of CJD in the differential diagnosis, and the diagnosis given back to the referring pathologist is the diagnosis submitted at the time of referral. Further histological investigations leading to an alternative diagnosis are the responsibility of the referring pathologist.

† Other forms of brain disease**:** ruptured atheromatous aneurysm (1); lymphocytic encephalitis ? viral (1); arteriosclerotic vascular dementia (1).

4.3 Protein Laboratory

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of CJD where frozen tissue is received by the National CJD Surveillance Unit. This is usually in the form of brain tissue obtained at autopsy, but occasionally brain biopsy or tonsil biopsy specimens are received. Small quantities of tissue are homogenized, treated with protease and the size and abundance of the three PrP^{res} glycoforms determined by Western blot analysis. The prion protein is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a PrP^{res} type where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. Type 2B has previously been found to be characteristic of variant CJD. A typical result is shown in Figure 13.

Figure 13 PrP^{res} Types in Sporadic and Variant CJD



Western blot analysis of protease-resistant prion protein (PrP^{res}) in two cases of sporadic CJD (sCJD) of the MM1 and VV2 subtypes and in a case of variant CJD (vCJD (MM2). The size of the nonglycosylated (bottom band) is either 21 kDa (termed type 1) or 19 kDa (termed type 2). Diglycosylated PrP^{res} (**) predominates in the variant CJD and the pattern is termed type 2B to distinguish it from type 2 cases in which the monoglycosylated form (*) predominates (type 2A).

A total of 33 UK cases with frozen tissue were received and analysed in 2004 and the results of the analysis are shown in Table 8:

Table 8 Breakdown of UK cases analysed in 2004

Diagnosis	Type	PrP^{res} +ve CNS
CJD	Sporadic	18/18
	Variant	2/2
	Iatrogenic	1/1
Alternative final diagnosis or not determined[1]		0/12

[1] includes two brain biopsies, two tonsil biopsies and an asymptomatic iatrogenic vCJD infection in an MV individual (Peden et al, Lancet 2004; 364: 527).

The cases that tested positive for PrP^{res} are further considered according to the results of PrP^{res} typing and genotyping of codon 129 of the prion protein gene *(PRNP)* in Table 9.

Table 9 PrP^{res} type/*PRNP* genotype breakdown of CJD cases received in 2004

Diagnosis	129	Type 1	Type 2A	Type 1 & Type 2[1]	Type 2B	Total
Sporadic CJD	M/M	10	-	-	-	10
	M/V	2	2	-	-	4
	V/V	-	3	1	-	4
	Total	**12**	**5**	**1**	-	**18**
Variant CJD[2]	M/M	-	-	-	2	**2**
Iatrogenic CJD[3]	M/M	1	-	-	-	**1**

[1]Mixed types are defined as cases where both Type 1 and Type 2 are found in the same sample from one part of the brain or where different types are found in samples from different brain regions.
[2] includes one case with a positive tonsil biopsy result but no autopsy tissue.
[3] Dura mater graft associated iatrogenic CJD.

Two additional requests for Western blot analysis were received from non-UK referrals. One was found to be type 2B and was confirmed as a case of variant CJD in a patient homozygous for methionine at codon 129 of *PRNP* and the other was a case of familial CJD with a V210I mutation, homozygous for valine at codon 129 of *PRNP* and a predominantly type 2 PrP^{res}.

4.4 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2004 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. A brain bank manager was appointed in 2002, who has primary responsibility for this unique resource. The activities of the Bank comply with current guidelines from MRC and the Royal College of Pathologists. The Bank and its activities are overseen by the Tissue Management Group established by the Department of Health.

4.5 Molecular Genetics

Familial CJD

Sixty-seven cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the National Prion Clinic in London). Of the 67 cases, 62 were resident in England and 5 were resident in Wales. Fifteen cases are still alive as at 31st December 2004. Thirty-seven of the cases had insertions in the coding region of the PrP gene, 16 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI) and one at codon 210 (Val-Ile). The remaining 11 were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (range 31-77 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 is 65% MM, 17% MV, 18% VV (see Table 10). There appears to be evidence ($p=0.013$) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2004. The explanation for this remains unclear and is being investigated further. It should be noted that not

all cases are genotyped (data available on 64%) and, therefore, changes in codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

Table 10 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2004

Deaths from sporadic CJD	MM(%)	MV(%)	VV(%)
Deaths from 1 May 1990 – 31 December 1995	97 (76)	14 (11)	17 (13)
Deaths from 1 January 1996 – 31 December 2004	212 (61)	65 (19)	69 (20)
Total	309 (65)	79 (17)	86 (18)
Genotype distribution for the normal population Pooling data from five studies	(39)	(50)	(11)

Codon 129 distribution in vCJD

All cases for whom genetic data are available (n=131, 86%) were methionine homozygotes at codon 129 of the PrP gene.

The genetic laboratory undertakes genetic analysis on a national and international basis.

4.6 CSF 14-3-3 and other brain specific proteins

The laboratory received 355 CSF samples from January 2004 – December 2004. Of these, 89 were from patients who were referred to NCJDSU as suspect cases of CJD and 213 were from patients who did not have clinical features to merit formal referral as a suspect case of CJD, but in whom the diagnosis remained a possibility. These are termed CSF only referrals. The remaining CSF samples were sent to the laboratory from hospitals outside the United Kingdom. The origin and numbers of these samples are given in Table 11.

Table 11 Number and origin of CSF samples received at the NCJDSU: Jan-Dec 2004

Source	Number of CSF samples (% of total)
CSF from suspect CJD referrals	89 (25%)
CSF only referrals	213 (60%)
Non-UK countries	53 (15%)
Total	355

The number of CSF-only referrals has increased by 39% whilst the number of CSF samples from suspect CJD patients referred to the NCJDSU has decreased by 19%. The numbers of CSF samples referred from non-UK countries more than doubled in 2004.

CSF 14-3-3 results in CSF samples received from suspect CJD patient referrals

The CSF 14-3-3 results in the remaining 89 patients are shown in Table 12.

Table 12 CSF 14-3-3 results in patients referred to NCJDSU: Jan– Dec 2004

Type of CJD	Diagnostic group (number of patients)	Positive 14-3-3/ Total number samples tested
Sporadic	Definite	16/16
	Probable	36/36
	Possible	0/2
	Not CJD	15/22
	Unknown classification	1/1
Variant	Probable	1/2
	Not CJD	1/4
Iatrogenic	Probable (hGH)	3/3
Genetic	Probable E200K mutation	1/1
	Unknown mutation	1/1
	Probable GSS (A117V)	0/1

Ten of the 36 patients with probable sporadic CJD are still alive, eight patients have died and are awaiting neuropathological examination and the remaining 18 patients have died without neuropathological confirmation of sporadic CJD. Of the patients who died without neuropathological confirmation of sporadic CJD, 4 patients had EEG traces that were considered typical for sporadic CJD whilst 10 had either EEG traces that were not considered typical or EEG traces that were not reviewed by the NCJDSU. Four EEGs are awaiting review. Therefore 14 of the 18 patients with probable sporadic CJD who died without neuropathological confirmation have been classified as probable on the basis of the 14-3-3 result, without independent EEG support.

There were 15 patients who were referred as suspect cases of CJD who had a positive 14-3-3 but were not diagnosed with CJD. In 13 patients the diagnosis remains a possibility (five of these patients have died without post mortem examination and 8 cases are still under review). In the remaining 2 cases, a diagnosis of Alzheimer's disease and viral encephalitis was made at post mortem.

CSF 14-3-3 in CSF only referrals

Two hundred and thirteen CSF samples were received as CSF only referrals and constituted 60% of the total number of samples received. As eight CSF samples were blood-stained only 205 were available for analysis. Seventeen of the 205 CSF samples analysed for CSF 14-3-3 were positive. The diagnoses of these cases are given in Table 13.

Table 13 Diagnoses in patients with positive 14-3-3 results in CSF only referrals

Diagnosis (number of patients)
Paraneoplastic syndrome (3)
Improved (2)
Central nervous system infection (2)
Vascular dementia (2)
Lewy body disease (1)
Siderosis (1)
Status epilepticus (1)
Acute disseminating encephalomyelitis (ADEM) (1)
Unknown (4)

One patient with definite sporadic CJD had a negative CSF 14-3-3. The CSF was sent as a CSF only referral and CJD was only confirmed at post mortem. At present, there is very little clinical information available.

In addition to the above samples, a set of 6 serial CSF samples were received from a patient undergoing pentosan polysulphate treatment.

The sensitivity, specificity, positive and negative predictive values for CSF 14-3-3 in the diagnosis of sporadic and variant CJD given in Table 14 are based on only 'definite CJD' and 'not CJD' cases.

Table 14 Sensitivity, specificity, positive and negative predictive values for CSF 14-3-3 for the diagnosis of sporadic and variant CJD, based on the 14-3-3 results for definite sporadic and probable variant CJD.

	Sporadic CJD Positive 14-3-3/ total numbers CSF investigated	Variant CJD Positive 14-3-3/ total numbers CSF investigated
Definite CJD	16/17	0/0
Probable CJD	36/36	1/2
Not CJD	15/22	1/4
Sensitivity	94%	50%
Specificity	32%	75%
Positive Predictive	52%	50%
Negative Predictive	88%	75%

Summary

The presence of 14-3-3 in the CSF in 14 patients with clinical features of sporadic CJD who died without postmortem and without typical EEG changes, has enabled these patients to be classified as probable sporadic CJD. Without CSF 14-3-3 analysis these patients would have remained as possible cases of sporadic CJD and would not have entered into the annual sporadic CJD figures. As sporadic CJD is a rare disease these 14 cases consititute a significant proportion, approximately 25%, of the annual number of cases.

The number of CSF samples received have increased, with the largest increase being samples received from patients without sufficient signs or symptoms to be considered a suspect case of CJD. This suggests that CSF 14-3-3 is increasingly being used as a screening test for CJD.

Section

5

NATIONAL CJD CARE TEAM

The national CJD Care Team is based within the National CJD Surveillance Unit and was formed in response to concerns regarding the care of CJD patients. An initial national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. Between March 2003 and November 2004 there were two co-ordinators and since November 2004 there has been one co-ordinator. The present team consists of one care co-ordinator and a secretary with clinical neurological support from within the Unit.

When a referral has been made to the NCJDSU of a likely case of CJD, the co-ordinator makes direct contact with the family and offers the opportunity to meet and to assist with care intervention. Referrals are also made to the Care Team from the National Prion Clinic at St Mary's Hospital and Leah Davidson, who co-ordinates the care of iatrogenic CJD cases. Once contact is made, the co-ordinator can meet with the patient and family on a regular basis, depending on need, to provide support and to assist with co-ordination of local health and social care professions. Post bereavement support is offered to the family after the patient dies or assistance given with accessing more specialised counselling.

The National CJD Care Team is in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist local authorities with the care of CJD patients. The National CJD Care Team is also responsible for the management of the CJD Advice Network. This is a group of Health and Social Services Professionals who have had experience of working with CJD and are available to share their experience and provide advice with other professionals. Audit is performed on contacts made to the Network and members will be kept up to date with recent developments within CJD with a six monthly newsletter.

From the establishment of the first National Care Co-ordinator post in 2000 until 31st December 2004, the care team have been in contact with, and/or provided access to care funds, to 74 variant cases, 73 sporadic cases, 20 familial cases and 11 iatrogenic cases.

The National Care Coordinators undertook 153 patient visits and case conferences during 2004. In addition, 17 teaching sessions were provided to professionals involved in the provision of care to CJD patients. In June 2004 a letter was sent to all neurology nurse managers offering a free teaching session on CJD by the care team. Twenty-seven positive replies came back of which 16 teaching sessions have been completed with 11 to be arranged in 2005.

Table 15 Family Visits, Case Conferences and Educational Sessions 1st January to 31st December 2004

Month	Cases Alive	Family Visits	Case Conferences	Educational Sessions
January	36	10	7	2
February	36	9	10	0
March	39	8	6	4
April	38	2	3	0
May	43	13	6	3
June	43	7	8	1
July	42	6	4	1
August	45	7	6	2
September	44	6	8	3
October	42	5	6	1
November	39	5	4	0
December	41	4	3	0

Table 16 Number of Cases with Family Visits and/or Case Conferences by subtype 1st January – 31st December 2004

Subtype of CJD*	No. of cases	No. of Family Visits	No. of Case Conferences	Average	
				Family Visits per case	Case Conferences per case
Variant	14	42	40	3	3
Sporadic	16	27	16	2	2
Familial/Genetic	7	13	15	3	3
Iatrogenic	0	0	0	-	-

*Variant, familial/genetic and iatrogenic cases are definite or probable cases by current definitions. Sporadic cases include initial involvement with 3 suspect cases that proved to be not CJD.

Table 17 Telephone Contact by Co-Ordinators 1st January 2004 – 31st December 2004

Subtype of CJD	No. of cases	No. of Calls	Time
Variant	14	322	64 hours
Sporadic	22	359	69 hours
Familial	15	139	23 hours
Iatrogenic	3	22	4 hours

Expenditure from the National CJD Care Fund to the end of December 2004 is £942,200, comprising £311,547 in 2004, £322,575 in 2003 compared with £243,476 in 2002 and £64,602 in 2001. A breakdown of expenditure during 2004 is shown in Table 18.

Table 18 Care Fund Payments
1st January – 31st December 2004

Description	Amount
Adaptations	20,996.54
Alternative Therapy	6,914.48
Care Hire	64,516.55
Childcare	778.81
Counselling	1,820.00
Equipment	38,326.47
Nursing	162,525.50
Physiotherapy	675.00
Respite	220.94
Social Care	12,253.84
Transport	2,519.10
TOTAL	**£311,547.23**

Section

6

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Section

7

Staff based at the National CJD Surveillance Unit, Western General Hospital, Edinburgh in 2004

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Dr RSG Knight	Consultant Neurologist
Professor JE Bell, Dr C Smith	Honorary Consultants in Neuropathology
Dr H Ward	Consultant Epidemiologist
Dr C Heath, Dr K Murray	Clinical Research Fellows
Mrs B Smith-Bathgate	Nurse Practitioner
Ms M Leitch	Research Nurse
Mr G McLean, Ms F Barnett	National Care Co-ordinators
Dr MW Head	Senior Research Fellow
Dr A Green	Senior Clinical Scientist
Mr M Bishop	Molecular Biologist
Ms J Mackenzie	Study Coordinator
Mr A Hunter	Business Manager
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Ms D Ritchie	Research Assistant
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