

CREUTZFELDT-JAKOB DISEASE SURVEILLANCE
IN THE UNITED KINGDOM

SECOND ANNUAL REPORT

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C O N T E N T S

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SECTION 1 CLINICAL SURVEILLANCE

INTRODUCTION

The national surveillance of Creutzfeldt-Jakob disease (CJD) was initiated in May 1990 and in the report of May 1992 information was provided on the retrospective survey between 1985 and 1990 and the first two years of the prospective study, May 1990 - April 1992. This report is an update of the prospective study covering the period May 1992 to 30 April 1993 and provides descriptive demographic information, analysis of the neuropathological aspects of the study and a preliminary analysis of the case-control study.

NUMBERS OF CASES

Between the start of the prospective study in May 1990 and 30 April 1993, 250 cases have been notified to the Surveillance Unit. 117 of these cases have been classified as definite or probable CJD according to previously described criteria and these cases are included in further analysis. The total number of cases by diagnostic category and the sources of notification are listed in Table 1.

53% of cases have been classified as "possible CJD" or "other" and this reflects the deliberate policy of requesting notification of any suspect case of CJD. This policy is important in order to avoid over selection of cases and inevitably results in a broad clinical spectrum of referrals. Neuropathological verification of the diagnosis is an essential component of the study, particularly in clinically borderline cases, and a post mortem rate of approaching 70% has been achieved in each year of the study (Table 1a).

Analysis of the number of definite and probable cases over the 3-year period of the prospective study shows an increase from 32 cases in the first year to 48 cases in the period 1st May 1992 to 30 April 1993. This increase is also apparent if the data is analysed by calendar year of death (Table 2). The total numbers of cases of CJD from 1970-1993 are represented in the histogram, Table 3 and the annual incidence from 1970-1993 in Table 4.

The increase in numbers of cases and annual incidence are not statistically significant. This reflects the rarity of CJD and the inevitable fluctuations from year to year. In the original grant application the power of the study was formally analysed and indicated that the incidence of CJD would have to double for a 5-year period to achieve statistical significance. Nonetheless, the increase in numbers of cases in the past 3 years is striking. The projection of 36 cases for the current year represent a drop from 1992 but this figure is likely to be an underestimate because of the lag in obtaining post mortem results. The likeliest explanation for the rise in numbers of cases over the 3 years of the study is increased case ascertainment, probably related to an increased awareness of CJD and of the National Surveillance Project. An analysis of the source of referrals does indicate an increased number of referrals from sources other than neurologists although the proportion of such referrals remains relatively constant (Table 5). It is also of note that 6 of the cases of CJD that died in 1992 were either iatrogenic or familial cases.

The incidence of CJD in 1992 of 0.86 should be considered in the context of the generally quoted incidence figure for CJD of 1 case/million/annum. Previous national surveys have shown an increase in the annual incidence as surveys proceed with a figure of 0.69 cases/million/annum in Chile between 1978 and 1983 and 1.07 cases/million/annum in Israel between 1963 and 1972. The increase in the number of cases of CJD in the United Kingdom should therefore be interpreted with great caution and in the context of other data available from the study.

CLINICAL FEATURES

CJD may present with a range of clinical signs. Rarely the initial clinical feature is predominantly cerebellar dysfunction, a syndrome originally described in 1965 by Brownell and Oppenheimer. In contrast, human growth hormone (HGH) recipients who subsequently develop CJD almost uniformly present with a cerebellar syndrome with cognitive impairment developing late in the clinical course, if at all. This contrasts with iatrogenic cases of CJD caused by neurosurgical cross contamination in which the clinical presentation closely parallels sporadic cases of CJD. The route of inoculation is the likeliest explanation for these disparate clinical features and this is potentially of relevance to assessing the risk of Bovine Spongiform Encephalopathy (BSE) as

any theoretical contamination of the human population would be more likely by a peripheral route. The proportion of cases of CJD with a predominantly cerebellar presentation has therefore been analysed (Table 6). This demonstrates that the number of cases with a cerebellar presentation are very low and are not increasing in proportion to the total number of cases. The numbers of cases of CJD with a cerebellar presentation are consistent with the findings before the occurrence of BSE and this does not suggest any change in the clinical features of CJD that might be attributable to BSE.

GEOGRAPHICAL DISTRIBUTION OF CASES

Table 7 presents the results of a Knox analysis of the last place of residence and date of death of 134 cases of CJD dying in Great Britain between 1 January 1985 and 30 April 1990, for evidence of space-time clustering. There is no evidence of space-time clustering in this series. There was a slight excess of pairs of cases with dates of death between 6 and 12 months apart and resident within 5 kilometres of each other, but the excess was not statistically significant ($p = 0.09$). Eight of these 13 pairs were formed by a cluster of 8 cases who died between May 1985 and July 1989 and were recorded as resident in Central London.

The geographical distribution of cases of CJD by place of residence at death for the period 1/5/90 to 30/4/93 is shown in Figure 1. Table 8 presents the results of a Knox analysis of last place of residence and date of onset (where known, otherwise date of death in 4 cases) of 65 cases of CJD in Great Britain notified after 30 April 1990 for evidence of space-time clustering. There was some evidence of an excess of pairs of cases with onsets 3 to 6 months apart and resident within 50 kilometres of each other ($p = 0.01$). Of these 42 pairs, 15 pairs (12 cases) forming one 'cluster' were resident in South East England in the London area, as far west as Windsor and as far south as Haywards Heath. Another 'cluster' of 13 pairs (11 cases) occurred in the North West of England in the Manchester and Liverpool areas, stretching as far east as Barnsley and as far north as Preston. This apparent space-time clustering should be interpreted with great caution. In the table, 20 different combinations of space-time cutoffs were examined and even in the absence of clustering one cell would be expected to be statistically significant at the 5% level.

Table 9 presents the results of Knox analysis of last place of residence and date of death (where known, otherwise date of death) of 313 cases of CJD in Great Britain with onset on or after 1 January 1980 for evidence of space-time clustering. No evidence of space-time clustering of cases was observed ($p > 0.05$ for all cells).

This data does not suggest any change in the geographical distribution of cases of CJD since the advent of BSE. It should be noted that a relatively high incidence of CJD was discovered in the Paris region in the study of CJD in France 1970-84 and in Santiago, Chile 1970-83, possibly attributable to increased ascertainment of cases in urban areas.

OCCUPATION

The Southwood Committee recommended that specific occupational groups should be monitored because of a theoretically increased risk from occupational exposure to the BSE agent. Because of the potentially prolonged incubation period in the spongiform encephalopathies, an assessment of occupational risk depends on obtaining information on occupational history rather than occupation at death. Out of 117 definite and probable cases in the prospective survey, detailed information on occupational history is available in 95. The numbers of cases with a history of employment in certain occupational groups of potential interest are listed in Table 10.

None of the individuals in the medical/paramedical/nursing/dentistry group had known contact with a case of CJD. Of the 8 individuals with a history of occupation in farming, 5 had been employed in farming decades prior to the occurrence of BSE and one further case had worked on a farm in Australia between 1968 and 1990. This patient had a known family history of CJD. A farmer's wife who was diagnosed in 1992 had worked on a small holding for over 20 years but there had not been a case of BSE in the herd (J. Wilesmith, Personal Communication). One further farmer (Case 148) who also died in 1992 had had a case of BSE in his herd and this occurrence has been published as a case report in the Lancet. In the context of previously published data on occupational risk in CJD and findings from previous surveys in England and Wales, this is most likely to have been a chance occurrence (see Appendix 1) rather than indicating any causal link with BSE. It is of note that the farmer

presented with a clinical picture typical of CJD and not with a progressive cerebellar syndrome.

Occupational risk is exceedingly difficult to assess from descriptive data in view of the rarity of CJD and the small occupational subset populations. The case-control study provides comparative data on occupational frequencies in cases and an age- and sex-matched control population. Case-control information is available in 89 patients and the results in relation to occupation are listed in Table 11. These figures do not suggest any significant increase in risk of developing CJD in association with any of the specified occupational groups.

In summary, current information does not suggest that occupation is linked to an increased risk of developing CJD and this includes occupations which might involve an increased exposure to the agent of BSE.

DIETARY FACTORS

Analysis of dietary factors in CJD is largely dependent on the case-control study although individual dietary histories may be of interest. For example, one individual who developed CJD has been identified who was a strict vegetarian for 20 years prior to death.

The high frequency of exposure to certain dietary factors in both cases and controls may preclude meaningful analysis of relative risk. Preliminary analysis of the intake of various types of meat (Table 12) shows no statistical difference between cases and controls. However the frequency of exposure, for example over 97% of both cases and controls had consumed beef, does not allow any meaningful formal analysis. On the other hand, statistical analysis is possible in relation to less commonly consumed meat products and some of these products, for example brain, are potentially of great interest in relation to BSE because certain tissues are likely to contain significant titres of infectivity (in contrast to beef).

Formal analysis has been carried out in the first 54 cases of CJD with comparable controls with respect to lifetime history of eating certain meat products. The analyses were performed using the computer package EGRET and all estimates take account of individual matching. The results of the

comparison of cases and controls with regard to lifetime consumption of meat products is shown in Table 13. There was no evidence that being reported to have ever eaten sausages, tripe, liver, sweetbreads, tongue, brains, trotters, haggis or heart was associated with an increased risk of CJD. (No cases or controls were reported to have eaten eyes). Cases were more likely to have been reported to eat kidneys than controls but this association was not statistically significant ($p = 0.11$). There was however some evidence of an association with ever having eaten 'puddings' (ie black or white puddings) and risk of CJD ($p = 0.02$), pudding eating apparently being associated with an approximately 3 fold increase in risk of CJD. The association between pudding eating and risk of CJD is examined in more detail in Table 14. When individuals reported never to have eaten 'puddings' are excluded from the analysis there is no evidence whatever of a trend towards increased risk of CJD associated with increased pudding consumption ($p = 0.76$). Table 15 shows the results of a comparison of cases and controls with regard to eating of meat products since 1985. No statistically significant associations were observed. Kidney eating and pudding eating were both reported more frequently among cases and controls, but neither association was statistically significant ($p = 0.07$ and $p = 0.12$) respectively).

In conclusion, we have found no convincing evidence that the eating of a range of meat products is associated with an increased risk of CJD. 'Pudding' eating appeared to be associated with risk of disease, but we could find no evidence of a dose response effect, and it should be borne in mind that 11 different meat products were examined. The nominal p value of this association ($p = 0.02$) should be treated with circumspection. On the other hand, the absence of any convincing association between these meat products and risk of disease does not mean that we can exclude the possibility of transmission occurring via this route. The sample size is relatively small, almost all cases and controls were reported to have been exposed to some of the products (eg sausages) whilst very few were reportedly exposed to others (eg sweetbreads). The study should nevertheless have reasonable power to detect large associations of public health importance for many of the products considered. No convincing evidence of such an association has been discovered.

MOLECULAR BIOLOGY

Since the start of the study, blood for DNA analysis has been obtained in all cases seen in life. A total of 97 samples have been analysed including 13 retrospective cases. 53 were analysed at the Prion Research Group at St. Mary's Hospital, London and 44 at the Centre for Genome Research in Edinburgh. 7 mutations of the prion protein gene have been identified including one retrospective case (Table 16). As mutations in the prion protein gene are thought to occur exclusively in familial cases of CJD, this gives a figure for the overall familial incidence of CJD of 12%.

The genotype at codon 129 of the open reading frame of the prion protein gene has been analysed in 49 sporadic cases of CJD (Table 17). The distribution of genotypes confirms the proposition that there is an excess of cases of CJD homozygous at codon 129 in comparison with the distribution of genotypes at codon 129 in the normal population. Furthermore, the clear excess of methionine homozygotes is consistent with a similar excess of this genotype in iatrogenic cases of CJD with a central route of inoculation. This finding is of potential importance in assessing the possibility of transmission of BSE to the human population. There is accumulating evidence that there is a relative excess of valine homozygotes at codon 129 in human growth hormone recipients in contrast to both sporadic CJD and cases of iatrogenic CJD due to central inoculation. A plausible explanation for this finding is that the genotype influences the likelihood of developing CJD in relation to the route of inoculation. The theoretical transmission of BSE to the human population would be more likely by a peripheral route of exposure. If this occurred evidence supporting it may come from the clinical presentation and from serially analysing the codon 129 genotype of sporadic cases of CJD in order to determine whether there is an increase in the proportion of valine homozygotes with time. There is currently no evidence of such a change.

The study of the molecular biology of CJD is an important component of the surveillance programme, but has raised difficult ethical issues. A meeting chaired by Professor Ingrid Allen was held in February 1993 under the auspices of the Medical Research Council in order to address the specific ethical issues raised by the surveillance programme. A careful and detailed discussion of the ethics of the surveillance programme has resulted in the formulation of defined policy in relation to the study of the molecular biology of CJD.

BIOMED 1 PROJECT FOR THE SURVEILLANCE OF CJD IN THE EUROPEAN COMMUNITY

A grant from the BIOMED 1 programme has been awarded between Dr RG Will and Professor A Hofman of Erasmus University, Rotterdam for the co-ordination of surveillance of CJD in the European Community. This project is potentially of great importance in assessing the epidemiological characteristics of CJD in the United Kingdom in comparison with other countries in the EC in which BSE has occurred either rarely or not at all. Factors of potential importance include relative national incidence figures, the occupational incidence in various countries and a case-control study of dietary factors in CJD. The study will allow any change in the epidemiological parameters of CJD in the UK to be put in the context of similar information from systematic epidemiological studies in other countries. The BIOMED 1 programme also has the potential to provide detailed scientific information on risk factors for CJD including analysis of molecular biological data on a large number of systematically ascertained cases.

Programmes for the surveillance of CJD are in place in France, Italy, Germany and Holland and it is likely that the co-ordination of surveillance programmes will be extended to Slovakia, Hungary and Poland.

CONCLUSIONS

The national surveillance programme for CJD in the United Kingdom has been running since May 1990. The information provided in this report indicates that a high level of case ascertainment has been achieved and detailed clinical and epidemiological information has been obtained in the great majority of cases. A high post mortem rate of approaching 70% has been maintained throughout the period of the study. The success of the project has been dependent on an extraordinarily level of co-operation from the neuroscience community and other medical and non-medical staff throughout the United Kingdom. We are particularly grateful to the relatives of patients for their help with the study.

Analysis of a variety of parameters shows no significant change in the epidemiological or clinical characteristics of CJD since the occurrence of BSE. There has been a rise in annual incidence but this is not statistically significant and is likely to be related to an increased ascertainment of cases. Nonetheless,

it is clearly important to ensure that there is no incremental rise in incidence of CJD over the next few years. Preliminary analysis of dietary history provides no significant evidence of an increase in incidence of CJD in relation to possible dietary exposure to BSE. Individuals potentially exposed to BSE through occupational contact have been identified but the frequency of such occupations is no different from control groups. The occurrence of CJD in a farmer who had a case of BSE in his dairy herd was most likely to have been a chance occurrence. Molecular biological investigation of CJD has provided important scientific information and no change in the relative proportions of specific genotypes that might be associated with BSE has been identified. The co-ordination of CJD surveillance programmes throughout the EC promises to provide important comparative information which may be crucial to an assessment of any change in the epidemiological parameters of CJD in the United Kingdom.

TABLE 1

1st May 1990 - 30 April 1993

250 suspected cases notified:

- 88 Definite
- 29 Probable
- 18 Possible
- 109 Other
 - 1 GSS
 - 5 Unclassified (identified from death certs and awaiting further information)

SOURCES OF CASES:

88 Definite

- 56 Neurologist
- 14 Pathologist
 - 5 General Physician
 - 6 Death Certificate
- 3 EEG
- 4 Other

29 Probable

- 19 Neurologist
- 3 General Physician
- 3 Death Certificate
- 1 Psychiatrist
- 2 EEG
- 1 Other

18 Possible

- 8 Neurologist
- 1 General Physician
- 4 Death Certificate
- 1 Psychiatrist
- 2 EEG
- 2 Other

109 Other

- 53 Neurologist
 - 9 Pathologist
 - 6 General Physician
- 23 Death Certificate
- 3 Psychiatrist
- 8 EEG
- 7 Other

1 GSS - Neurologist

5 Not Classified - Death Certificates

TABLE 1A

Number of deaths from suspect CJD and post mortem percentage (%)
conducted by year (1 May - 30 April)

Year	No. of Deaths	PMs Performed	%
1991	61	41	67
1992	66	45	68
1993	77	53	69

TABLE 2

Breakdown of Definite and Probable cases over the 3 year period

1 May 1990 - 30 April 1991	32
1 May 1991 - 30 April 1992	37
1 May 1992 - 30 April 1993	48
Total	117

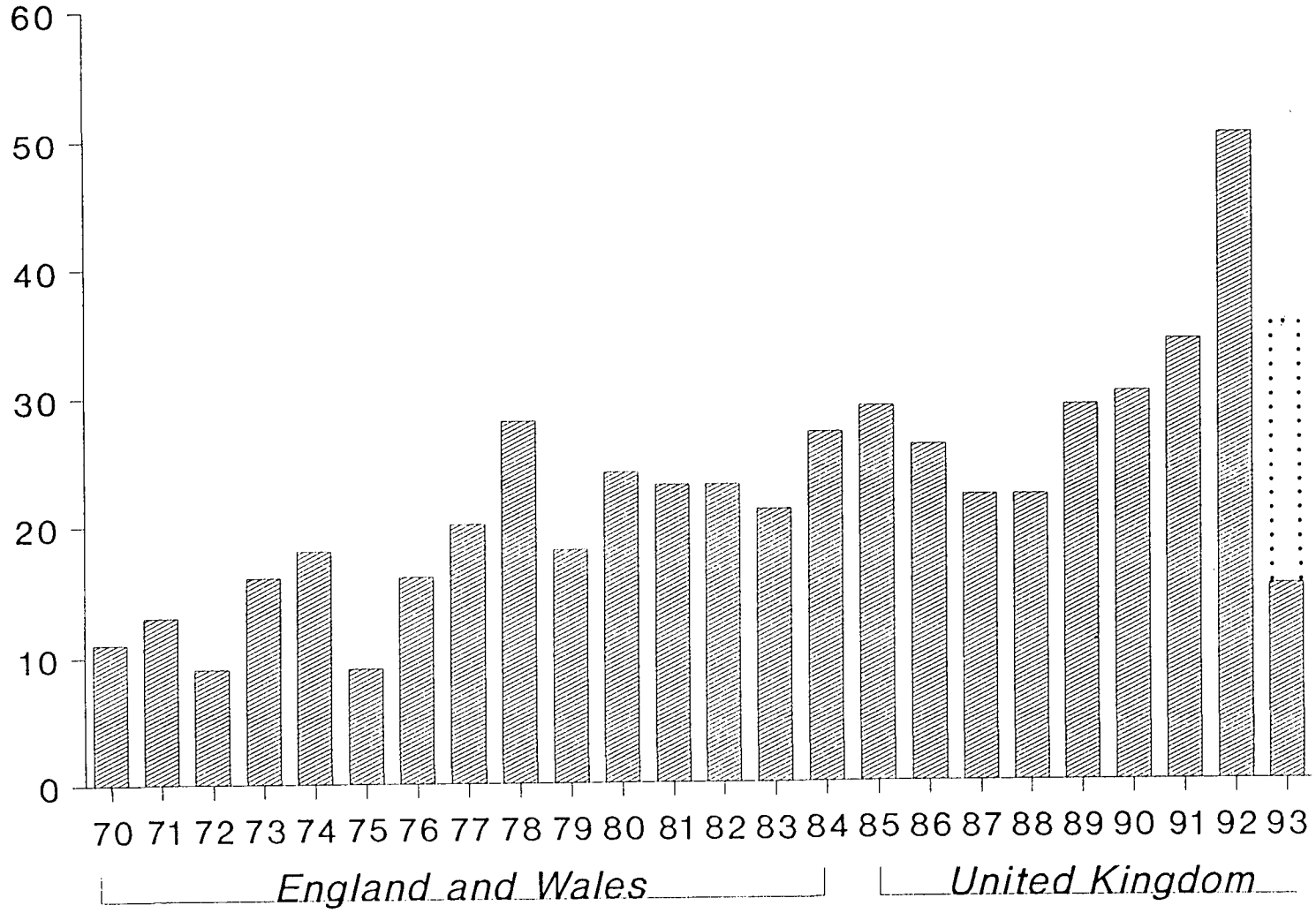
Definite and Probable cases by year of death

1 January - 31 December 1990	30	[12 from 1 Jan - 30 April 18 from 1 May - 31 Dec]
1 January - 31 December 1991	34	
1 January - 31 December 1992	50	
1 January - 31 May 1993	10 + 5 Probable still alive	

DEATHS FROM CJD
 (DEFINITE & PROBABLE CASES)
 1970 - 1993

TABLE 3

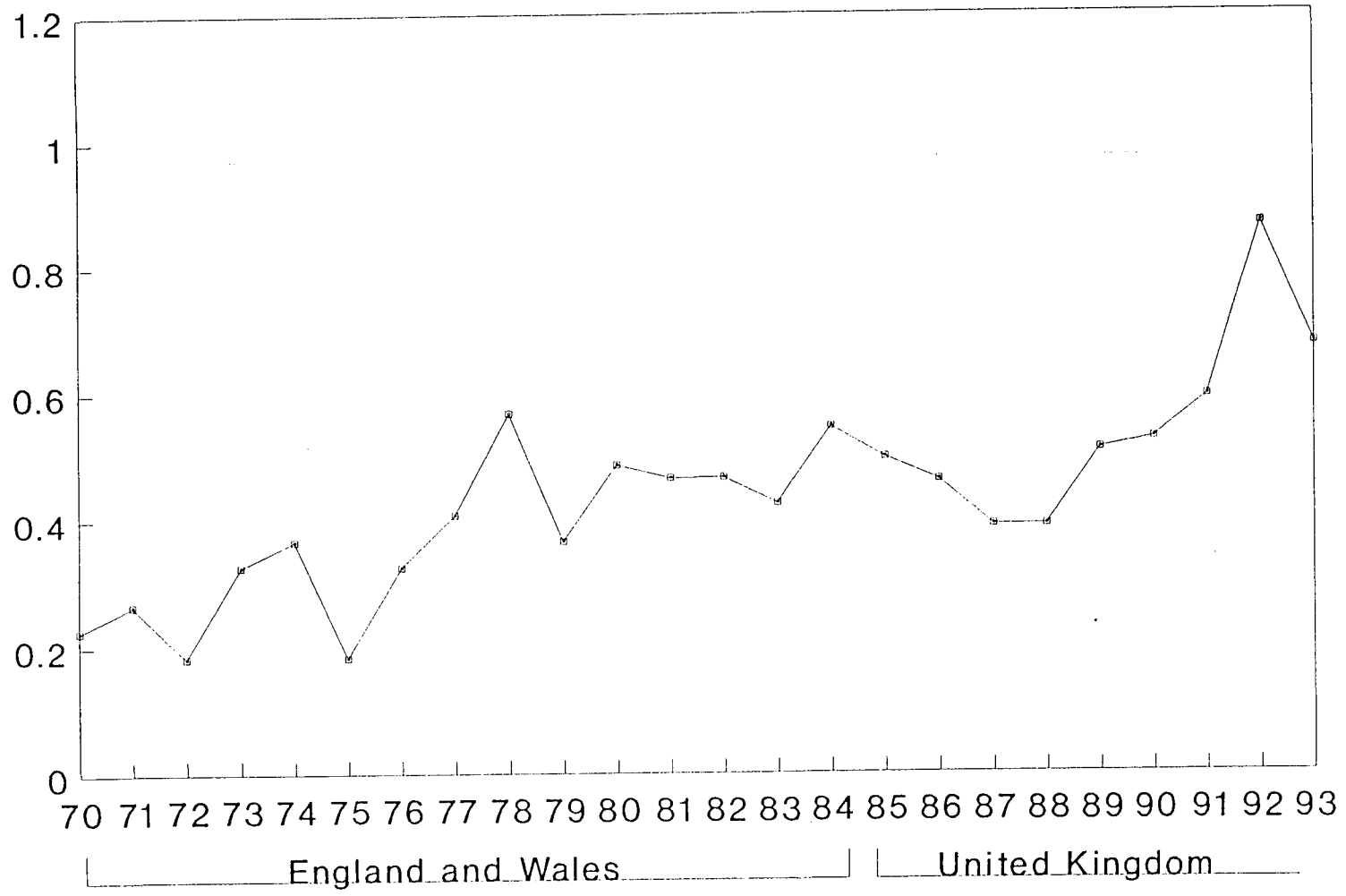
14



INCIDENCE (PER MILLION) OF CJD
DEFINITE AND PROBABLE
1970 - 1993

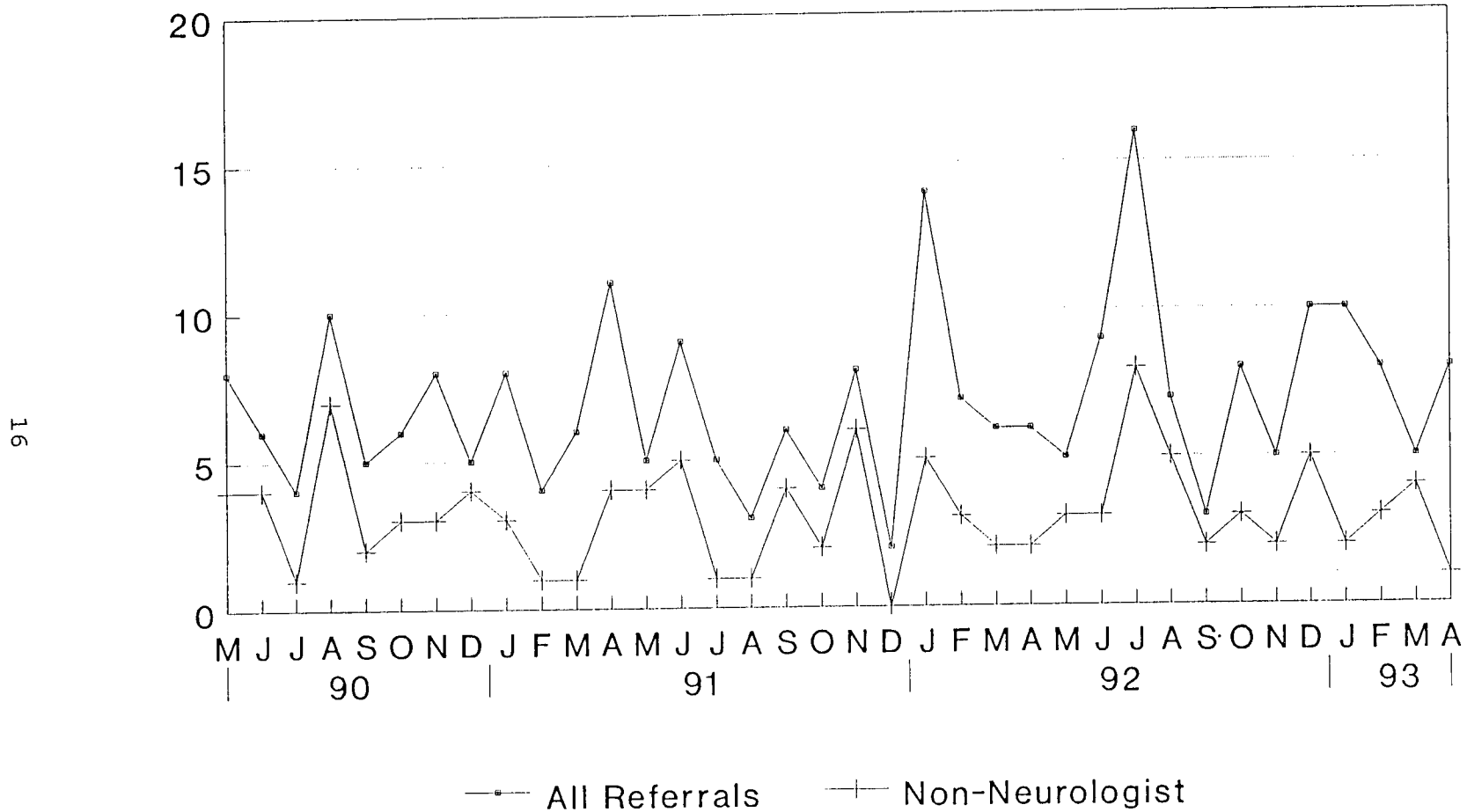
TABLE 4

15



NUMBER OF REFERALLS PER MONTH TO THE CJD SURVEILLANCE UNIT

TABLE 5



1 MAY 1990 - 30 APRIL 1993

TABLE 6

Cases of CJD with a cerebellar presentation (including HgH recipients)

Year of Notification	Definite	Probable	Possible
1990 (from 5/90)	3 (1 HgH*, 1 HGnH**) [15]	1 (1 HgH) [3]	0 [4]
1991	1 [28]	0 [6]	0 [4]
1992	3 (2 HgH) [40]	2 [14]	0 [3]
1993 (to 4/93)	0 [5]	0 [6]	2 [7]

Figures in brackets are total numbers of cases in each group

* HgH: human growth hormone recipient

** HGnH: human gonadotrophin recipient

TABLE 7

Results of a Knox analysis of 134 cases of Creutzfeldt-Jakob disease dying in Great Britain between 1/1/85 and 30/4/90 (excludes 1 case in Jersey and 4 cases in Northern Ireland)

Time * between dates of onset	Distance between places of residence at onset							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	1	1.8	3	3.7	10	8.6	21	22.7
1-3 months	3	3.0	10	6.3	15	14.4	40	38.2
3-6 months	2	4.5	6	9.4	14	21.7	44	57.7
6-12 months	13	8.5	23	17.8	43	40.9	105	108.6
1-2 years	17	13.5	30	28.3	74	65.2	163	173.2
2-3 years	8	10.4	19	21.7	52	50.0	148	132.8
3-4 years	7	7.8	16	16.2	36	37.3	103	99.2
4-5 years	3	4.1	5	8.6	14	19.7	57	52.3

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

Figure 1

CREUTZFELDT-JAKOB DISEASE IN THE UNITED KINGDOM
DEATHS IN THE PERIOD 1 MAY 1990 - 30 APRIL 1993
DEFINITE AND PROBABLE CASES



TABLE 8

Results of a Knox analysis of 65 cases of Creutzfeldt-Jakob disease in Great Britain notified after 30/4/90 (excludes two cases with missing data)

Time * between dates of onset	Distance between places of residence at onset							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	0	0.8	0	1.6	1	5.0	8	13.9
1-3 months	2	1.0	2	2.2	7	6.8	20	18.6
3-6 months	1	1.6	6	3.4	9	10.6	42	29.1*
6-12 months	2	2.8	5	5.9	23	18.3	54	50.3
1-2 years	2	3.1	4	6.5	17	20.2	41	55.6

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

* $p < 0.05$

TABLE 9

Results of a Knox analysis of 313 cases of Creutzfeldt-Jakob disease in Great Britain with onset on or after 1st January 1980

Time * between dates of onset	Distance between places of residence at onset							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	4	3.7	9	7.5	25	20.8	61	65.2
1-3 months	6	5.4	13	11.0	24	30.7	88	96.1
3-6 months	10	8.3	19	16.9	37	47.0	161	147.1
6-12 months	15	16.1	29	32.8	97	91.4	261	286.1
1-2 years	23	29.9	46	60.8	160	169.6	521	530.6
2-3 years	21	27.1	50	55.0	161	153.6	465	480.5
3-4 years	24	24.0	56	48.9	143	136.3	420	426.5
4-5 years	28	21.1	45	42.9	110	119.6	367	374.3
5-6 years	26	19.3	48	39.1	119	109.2	359	341.6
6-7 years	15	16.4	32	33.4	94	93.2	285	291.6
7-8 years	16	14.0	34	28.4	87	79.2	259	247.8
8-9 years	9	10.9	21	22.2	56	61.9	210	193.6
9-10 years	5	8.6	12	17.5	39	48.9	143	152.9

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

TABLE 10

OCCUPATIONAL HISTORY

Out of 117 Definite and Probable cases, we have detailed occupational histories on 95:

- 9 Medical/Paramedical/Nursing/Dentistry
- 1 Animal Laboratory
- 0 Pharmaceutical Laboratory
- 0 Research Laboratory
- 8 Farmers/Veterinary Surgeons
- 5 Butchers/abattoir workers or occupation involving direct contact with animals/carcasses
- 9 Occupation involving animal products

Medical/Paramedical/Nursing/Dentistry

- Case 1 Health Clinic cleaner
- Case 7 Nurse
- Case 10 Nursing auxillary
- Case 14 Nursing auxillary in theatres
- Case 50 Doctor's receptionist/records
- Case 73 Hospital domestic
- Case 105 Hospital dietician
- Case 115 Nurse
- Case 196 Assistant in children's/elderly home

Animal Laboratory

- Case 86 Animal laboratory assistant (School) 1958-1979

Farmers/Veterinary Surgeons

- Case 56 Farmhand pre 1949
- Case 136 Farm worker pre-war
- Case 165* Farm worker Australia 1968-90
- Case 201 Farmer's wife to 1954 & 1960-1992
(no known case of BSE in herd)
- Case 155 Farm worker around 1945
- Case 146 Farm worker 1928-1940
- Case 148 Farmer 1945 - Death
(known case of BSE in herd)
- Case 213 Crofter around 1943

*Familial case.

Butchers/abattoir workers or other occupation involving direct contact with animals/carcasses

- Case 110 Pet shop/Gardening shop 1940
- Case 147 Shopkeeper - prepared meat 1947-1991
- Case 178 Prepared meat (boning & rolling) 1960-1979
- Case 223 Ham curer 1974-1983
- Case 172* Kitchen assistant - prepared meat 1977-1992

* Familial Case.

Occupation involving animal products

- Case 10 Sausage factory worker pre-1978
- Case 89 Warehouse foreman in wool factory 1957-1990
- Case 44 Manufacturing pig meat products 1935-47 & 1970-75
- Case 74 Wool packer 1976-1985
- Case 210 Tan yard 1958-1960
- Case 178 Milkman 1979-1983
- Case 221 Weaver 1942-1965
- Case 132 Woolmill 1957-1963
- Case 153 Cattle feed production 1958

TABLE 11

CASE-CONTROL INFORMATION ON OCCUPATION - AVAILABLE ON 89 PATIENTS

	<u>Cases</u>	<u>Controls</u>
Medical/Paramedical/Nursing/Dentistry	7	8
Animal Laboratory	1	0
Pharmaceutical Laboratory	0	0
Research Laboratory	0	0
Farmers/Veterinary Surgeons	7	6
Butchers/abattoir workers or occupation involving direct contact with animals/carcasses	5	3
Occupation involving animal products	9	6

TABLE 12

Case and Control Data for Dietary History

Cases (n = 89)

	Yes	No	No Info
Lamb/mutton	88	0	1
Pork/bacon/ham	88	0	1
Beef	88	0	1
Venison	21	64	4
Veal	25	60	4
Poultry	86	0	3
Fish	86	1	2

Controls (n = 89)

	Yes	No	No Info
Lamb/mutton	82	5	2
Pork/bacon/ham	85	2	2
Beef	86	1	2
Venison	14	75	0
Veal	16	72	1
Poultry	87	0	2
Fish	86	0	3

TABLE 13

Results of a comparison between 54 cases of Creutzfeldt-Jakob disease, post April 1990 and their matched controls with regard to lifetime history of eating meat products

Type of product	Consumed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value
Sausage	No	0 (0)	2 (4)	1.0		
	Yes	52 (100)	51 (96)	∞	(0.19, ∞)	0.50
Tripe	No	39 (72)	40 (74)	1.0		
	Yes	15 (28)	13 (26)	1.25	(0.49,3.17)	0.64
Liver	No	9 (17)	7 (13)	1.0		
	Yes	45 (83)	46 (87)	0.88	(0.32,2.41)	0.80
Kidney	No	16 (30)	24 (44)	1.0		
	Yes	38 (70)	30 (56)	1.89	(0.84,4.24)	0.11
Sweetbreads	No	50 (96)	51 (94)	1.0		
	Yes	2 (4)	3 (6)	0.67	(0.11,3.99)	0.65
Tongue	No	23 (44)	29 (54)	1.0		
	Yes	29 (56)	25 (46)	1.56	(0.67,3.59)	0.30
Brains	No	51 (94)	48 (89)	1.0		
	Yes	3 (6)	6 (11)	0.50	(0.13,2.00)	0.31
Trotters	No	44 (83)	46 (87)	1.0		
	Yes	9 (7)	7 (13)	1.29	(0.48,3.45)	0.62
Puddings	No	18 (34)	30 (56)	1.0		
	Yes	35 (66)	24 (44)	2.71	(1.14,6.46)	0.02
Haggis	No	39 (75)	42 (78)	1.0		
	Yes	13 (25)	12 (22)	1.11	(0.45,2.73)	0.82
Heart	No	43 (80)	39 (75)	1.0		
	Yes	11 (20)	13 (25)	0.78	(0.29,2.09)	0.62

TABLE 14

Results of a comparison between 54 cases of Creutzfeldt-Jakob disease and their age and sex matched controls with regard to 'pudding' consumption

Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.
Never	18 (34)	30 (56)	1.0	
< 1/year	9 (17)	3 (6)	∞	(0.66, ∞)
> 1/yr	18 (34)	14 (26)	2.40	(0.79,8.70)
> 1/month	8 (15)	7 (13)	1.50	(0.17,18.0)
Test for trend, all levels, $p = 0.07$				
Test for trend, excluding "never" group, $p = 0.76$				

TABLE 15

Results of a comparison between 54 cases of Creutzfeldt-Jakob disease, post April 1990 and their matched controls with regard to eating meat products since 1985

Type of product	Consumed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value
Sausage	No	3 (6)	3 (6)	1.0		
	Yes	50 (94)	50 (94)	1.0	(0.20,4.95)	1.00
Tripe	No	46 (85)	45 (85)	1.0		
	Yes	8 (15)	8 (15)	1.0	(0.35,2.85)	1.00
Liver	No	11 (20)	9 (17)	1.0		
	Yes	43 (80)	44 (83)	0.90	(0.37,2.22)	0.82
Kidney	No	18 (33)	28 (52)	1.0		
	Yes	36 (67)	26 (48)	2.00	(0.94,4.27)	0.07
Sweetbreads	No	51 (98)	53 (98)	1.0		
	Yes	1 (2)	1 (2)	1.00	(0.06,16.0)	1.00
Tongue	No	26 (50)	34 (63)	1.0		
	Yes	26 (50)	20 (37)	2.00	(0.81,4.96)	0.12
Brains	No	53 (98)	53 (98)	1.0		
	Yes	1 (2)	1 (2)	1.00	(0.06,16.0)	1.00
Trotters	No	49 (92)	52 (96)	1.0		
	Yes	4 (8)	2 (4)	2.00	(0.37,10.9)	0.41
Puddings	No	23 (43)	31 (57)	1.0		
	Yes	30 (57)	23 (43)	1.89	(0.84,4.24)	0.12
Haggis	No	40 (77)	44 (81)	1.0		
	Yes	12 (23)	10 (19)	1.29	(0.48,3.45)	0.62
Heart	No	50 (93)	47 (89)	1.0		
	Yes	4 (7)	6 (11)	0.60	(0.14,2.51)	0.48

TABLE 16

ORF Mutations - 7 cases (12% of definite and probable cases)

<u>Mutation</u>	<u>Codon 129</u>	<u>FH</u>	<u>O/D*</u>	<u>Clin.</u>	<u>Path.</u>
178Asn	MM	N	61/14	Insomnia	Thalamic gliosis
200Lys	MM	Y	67/1	Classic	Sponge
RptIns	MM	N	56/3	Classic	Sponge
200Lys	MM	Y	57/4	Classic	Sponge
200Lys	MM	?Y	46/19	Psychiatric	Sponge
?RptIns	MV	Y	46/3	Heidenhain	Sponge
200Lys	MM	Y	57/4	Classic	Awaited**

*O = Onset (years)
D = Duration (months)

** Retrospective

ORF: open reading frame of the prion protein gene
FH: family history
M: methionine
V: valine

TABLE 17

Genotype at Codon 129 of 49 sporadic cases

<u>Genotype</u>	<u>"Expected" frequency</u>	<u>Frequency</u>
MM	37%	73%
MV	51%	10%
VV	12%	16%

M: methionine
V: valine

SECTION 2

NEUROPATHOLOGICAL VALIDATION

1. Statement of progress

The second year of the CJD neuropathology surveillance project is now complete. This project includes neuropathological examination, and validation of diagnosis, in cases referred to us either for full autopsy or for detailed brain examination following autopsy elsewhere in the country. A formal collaboration has been established with Dr J. McLaughlin at the Royal Free Hospital, London, to whom cases in and around London may be referred in the event of difficulty regarding autopsy. A less formal network of collaborating pathologists exists around the country and arrangements for autopsy in cases of suspected CJD do not usually present any difficulty. Cases in central Scotland continue to be transferred to Edinburgh and this provides an opportunity for wide ranging neuropathological examination. Both the consultant neuropathologists, Dr James Ironside and Dr Jeanne Bell participate in the surveillance project, assisted by a full-time MLSO 2 technician. Secretarial support is provided by 2 half time secretaries. The surveillance project, including support for the non-medical staff, is funded by the Department of Health and the Scottish Home and Health Department. A programme of research in human spongiform encephalopathies has now been established, funded by the Medical Research Council and the Agricultural and Food Research Council. These grants support 2 Post-Doctoral scientists, Dr K. Sutherland and Dr I. Goodbrand, and 2 further technical staff. The aim of the research programme is to map the distribution of the abnormal prion protein within the central nervous system of affected individuals; to investigate the associated tissue damage and cellular reactions; and to correlate these with the clinicopathological findings. Reliable methods for the demonstration of abnormal prion protein have now been established and work is in progress to demonstrate the protein at the sub-cellular level. A range of antibodies obtained from different centres, including the Institute for Animal Health AFRC/MRC Neuropathogenesis Unit, Edinburgh, is now in regular use.

With regard to health and safety issues, containment and decontamination procedures have been reviewed periodically both as a matter of policy, and in view of the recent EC decision to regroup the human spongiform encephalopathy agents into category 3. The Edinburgh CJD laboratory currently operates at a containment level of 2 + +. We have now instituted an annual shut down of the laboratory for a very thorough period of decontamination, and safety protocols are continually reviewed in the light of advancing knowledge. It is expected that the CJD laboratory will seek accreditation as part of a review of laboratories

within the Western General hospital. At a national level, Dr J. Bell remains a member of the ACDP Working Party on Spongiform Encephalopathies whose recommendations are near completion. Preliminary advice has been issued by the working party in the form of a Professional Letter (PL (92) CO/4). Further comprehensive advice should become available shortly, all with the purpose of reducing the possibility of iatrogenic transmission.

2. Collaboration with other centres.

Close collaboration has been maintained with the Neuropathogenesis Unit, University of Edinburgh, particularly with regard to the supply of antibodies to the prion protein. We are particularly grateful to Dr J. Hope and his colleagues in this matter. Dr I. Goodbrand has received training in electronmicroscopy and immunoelectronmicroscopy by staff working in the Neuropathogenesis Unit and a close collaboration has been established for ultrastructural studies on both human and animal material.

In March 1993, Dr J. Ironside, Dr K. Sutherland and Ms C. Barrie attended the annual AFRC meeting on the programme of research into spongiform encephalopathies in animals and humans. An update on progress on the grant-funded research in the CJD Surveillance Unit was presented, and collaborative research links were established with other members of the AFRC, particularly in relation to the investigation and production of antibodies to the prion protein.

In April 1993, the CJD Surveillance laboratory hosted a workshop on prion protein immunocytochemistry. This was funded by the Medical Research Council and provided an opportunity for active workers in the field to meet and discuss the problems and interpretation of this technique. The meeting was chaired by Professor Ingrid Allen. Further exchange of material and information between centres in Edinburgh, London, Nottingham and Belfast is expected as a result of this meeting.

In May 1993 Dr Bell, Dr Goodbrand and Dr de Silva attended the Prion meeting arranged by Dr J. Collinge at the Royal College of Physicians.

EC Concerted Action on CJD surveillance. A number of centres in the community have established a surveillance programme, similar to the one operating in the UK. Furthermore, a proposed concerted action on neuropathology in human spongiform encephalopathies has been considered by the Community and a preliminary meeting was held in Brussels in April 1993 to discuss this possible venture. Dr J. Ironside attended the meeting as a representative of the UK

National Surveillance Programme, and presented information relating to the working of the surveillance programme with particular emphasis on the laboratory aspects of tissue handling, staining, histopathological interpretation and diagnostic criteria. This proposed concerted action is still under consideration by the Community. The surveillance programme in the UK is recognised as a model on which other surveillance programmes may be based in Europe. In this respect, the UK Surveillance Unit has received a steady referral of cases from other EC countries for confirmation of the diagnosis of human spongiform encephalopathy and prion protein immunostaining. It is anticipated that this role as a reference centre for the Community will expand in the near future.

Visitors to the CJD laboratory have included pathology colleagues and representatives from the National Health and Safety Executive.

3) Surveillance and workload during 1992-93

Total cases examined	80
Animal material	4
CJD cases from EC	5
Historical CJD cases	4
CJD cases for immunocytochemistry	6
Growth hormone recipients (not with CJD)	2
Suspected sporadic CJD cases (including 1 growth hormone recipient)	59

After macroscopic and histological examination of the 59 suspected CJD cases the following diagnoses were made:

Creutzfeldt-Jakob disease	38
Alzheimer's disease	11
Atypical dementias	5
Other disorders (including hypoxic brain damage, cerebral abscesses, viral encephalitis)	5

The overall number of cases examined has increased slightly in comparison with last year's figures, but the number of cases confirmed as CJD is broadly similar to the previous year, bearing in mind that the figure for confirmed cases in the previous annual report included archival material from cases ascertained in the last 5 years.

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APPENDIX 1

CREUTZFELDT-JAKOB DISEASE IN AN INDIVIDUAL OCCUPATIONALLY EXPOSED TO BOVINE SPONGIFORM ENCEPHALOPATHY

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R.G. Will.

INTRODUCTION

The occurrence of bovine spongiform encephalopathy (BSE) has led to public and professional concern regarding the possibility of a risk to human health. In 1989 an expert committee (The Southwood Committee) made a number of recommendations in response to the advent of BSE,¹ including the re-institution of surveillance of Creutzfeldt-Jakob disease (CJD) in the United Kingdom with particular reference to occupational groups theoretically at a higher risk from BSE, because of fears that there might be transmission to man. In the course of the national surveillance programme, we have identified an individual with pathologically confirmed CJD who had previously had occupational contact with a case of BSE and, although no definite conclusion is possible, we believe we should report the case and our view of its significance.

CASE REPORT

A 61-year old right handed man was admitted for investigation of progressive dysphasia. Twelve months prior to admission he had suffered an episode of acute loss of consciousness with features suggestive of syncope. A few months later he had an episode of involuntary movement in which the left arm reached behind his back and grabbed his right arm. This was not associated with loss of consciousness. He had one further similar bout of involuntary movement approximately a month later. He was then well until four weeks prior to admission when he described loss of the sense of smell. This gradually resolved but concurrently he developed increasing difficulties with his speech and felt that his short term memory had become less reliable. He was admitted to hospital for investigation.

On examination, he was alert and mildly euphoric. There was an expressive dysphasia, dysgraphia, constructional dyspraxia and mild impairment of short term memory. Cranial nerves were normal. In the motor system, the only abnormality was reduction in dexterity in the right hand and there were no involuntary movements.

Routine biochemical and haematological investigations were all normal and VDRL, TPHA and HIV screening tests were negative. CT brain scan showed a mildly enlarged ventricular system and mild cortical atrophy. The cerebrospinal fluid was normal. Initial electroencephalogram showed continuous high amplitude slow activity in the right hemisphere but serial recordings revealed triphasic generalised periodic complexes at approximately one per second consistent with the diagnosis of CJD.

During admission there was a rapid deterioration with increasing dysphasia and ataxia and within three weeks akinetic mutism had developed. This was associated with frequent myoclonic jerks and several generalised seizures. After a prolonged period of immobility, the patient developed bronchopneumonia and died three months after the initial hospital admission.

Post mortem was performed and macroscopic examination of the brain revealed marked atrophy of the occipital cortex particularly around the calcarine sulcus but no evidence of widespread cerebral or cerebellar atrophy. The brain weighed 1436g. Histological examination of paraffin-embedded tissue sections showed widespread spongiform change throughout the cerebral cortex, with particularly severe changes in the occipital lobe. In this region, spongiform change was accompanied by widespread neuronal loss and florid reactive gliosis. Spongiform change was also noted in the basal ganglia, thalamus, hypothalamus and cerebellum in a patchy distribution. Immunocytochemistry for prion protein (1A8 antibody, courtesy of Dr J. Hope, Neuropathogenesis Unit, Edinburgh) showed intense staining in the neuropil adjacent to areas of spongiform change, particularly in the occipital lobe. No other significant histological abnormalities were detected. The neuropathological findings were typical of CJD.

The patient had been treated for hypertension for the preceding 18 months and had undergone an operation for intestinal volvulus as an infant. There was no history of previous neurosurgery and no family history of dementia. The open reading frame of the prion protein gene was sequenced at the Centre for Genome Research, Edinburgh and this was entirely normal, excluding any of the known pathogenic mutations associated with familial CJD.

The patient had been employed as a dairy farmer throughout his working life and in 1989 had had a case of BSE in his dairy herd. The diagnosis of BSE was confirmed histologically (J. Wilesmith, CVL, Personal Communication). The affected animal was a previously healthy 7-year old Friesian that had been potentially exposed to contaminated feed prior to July 1988 when the feeding of ruminant proteins to cattle was banned. The farmer had been in contact with the animal throughout its life in the context of normal animal husbandry but had had no contact with internal organs/tissues, for example in assisting veterinary surgery or at the time of the animal's slaughter. He had drunk pooled milk from the herd which included that from the affected animal.

DISCUSSION

This is the first reported case of CJD in an individual with direct occupational contact with a case of BSE and raises the possibility of a causal link between the two conditions. It is however impossible to reach any definitive conclusions on the basis of one case and clinicopathological and epidemiological evidence suggests that the apparent link is likely to be a chance phenomenon.

Occupation as a risk factor for CJD has been examined in systematic surveys, prior to the advent of BSE, both in England and Wales² and in other countries. No significant occupational risk has been identified in any of these studies but it is of note that in the case-control study in England and Wales between 1980-84², six patients with CJD had been employed in farming at some time in their lives all clearly prior to the advent of BSE. Since May 1990, incident cases of CJD in the United Kingdom have been included in a case-control study with reference to risk factors including occupation. Up to the present time, 64 patients have been entered into this study of whom 4 with CJD have a history of occupation in farming (the current case plus 3 other individuals who had worked in farming decades before the advent of BSE) and 5 control patients with an occupational history of farming. Epidemiological surveys prior to the occurrence of BSE and the current survey since the advent of the BSE epidemic do not suggest that an excess of individuals are developing CJD.

115,316 individuals are employed in dairy farming in England and Wales (1991 Census) and over one third of farms have had at least one case of BSE. As a sporadic phenomenon with an incidence of 0.5 cases/million/annum, CJD will inevitably occur in this occupational group as a chance phenomenon and by crude calculation, the

likelihood of such a case being identified in the first two and a half years of the current survey is approximately 0.1 (ie observed incidence 10 times expected incidence). However, as Dr Paul Brown has pointed out³, meaningful conclusions in relation to the relative risk of occupation in CJD cannot be drawn whatever statistical tests are used because of the small numbers of cases and small "subset" populations. In the study of CJD in France³ there was an "elevated" incidence rate of 3.08/million in priests and nuns, occupations with no putative risk for CJD and in the current study of CJD in the UK, individuals have been identified with occupations for example vicar, art teacher, which are statistically less likely to have occurred by chance than potentially "at-risk" occupations such as farming.

From a clinical perspective, the evolution of symptoms and signs in the present case, the investigations including the EEG, and the post mortem findings, are entirely consistent with previous experience in CJD.⁴ Episodic involuntary movements prior to the development of overt progressive disease are not a commonly recognised feature of CJD but were present in 5/158 cases in a previous survey of CJD.⁴ Other risk factors for CJD including iatrogenic transmission and genetic predisposition have been largely excluded by the history and gene analysis. The Southwood Committee recommended surveillance of specific occupational groups because of the risk of direct inoculation of bovine tissue. The available history does not suggest any such occurrence in this particular case and the only possible direct route of cross-contamination was by ingestion of milk. Milk does not contain detectable titres of infectivity even from animals clinically affected with natural diseases^{5,6} and epidemiological evidence, for example the absence of vertical transmission in kuru despite breast feeding of infants by affected mothers,⁷ largely precludes milk as a route of transmission in spongiform encephalopathies.

In conclusion, the occurrence of CJD in this case is most likely to have been a chance phenomenon and a causal link with BSE is at most conjectural. It is however crucially important to obtain further scientific evidence on the characteristics of the transmissible agent in this case which may allow a more definitive judgement as to the source of the transmissible agent.

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