CREUTZFELDT-JAKOB DISEASE SURVEILLANCE

IN THE UNITED KINGDOM

THIRD ANNUAL REPORT

SEPTEMBER 1994

The National CJD Surveillance Unit
Western General Hospital
Crewe Road, Edinburgh, EH4 2XU

CONTENTS

	PAGE NO.
Clinical Surveillance	3-31
Figures	32-46
Neuropathological Validation	47-51
Publications	52-55
Project workers	56
Appendices	57

SECTION 1 CLINICAL SURVEILLANCE

INTRODUCTION

The national surveillance of Creutzfeldt-Jakob disease (CJD) was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (The Southwood Committee) and is funded by the Department of Health and the Scottish Home and Health Department. The primary aim of the project is to monitor CJD in order to identify any change in the pattern of this disease that might be attributable to the emergence of Bovine Spongiform Encephalopathy (BSE). Two previous annual reports were published in 1992 and 1993 and this report documents the findings from the CJD Surveillance Project up to 30th April 1994.

NUMBERS OF CASES

Between the start of the prospective study in May 1990 and 30th April 1994, 316 suspected cases have been notified to the surveillance unit. 159 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.

As in the last report, approximately 50% of all notified cases have been classified as 'possible' CJD or 'other', reflecting the deliberate policy of requesting notification of any suspect case of CJD. Figure 1 illustrates the breakdown by diagnostic category and also lists the cases of suspect CJD in which alternative diagnoses have been made following neuropathological examination.

The numbers of cases of definite and probable CJD increased between 1990 and 1992 but there has been a small drop in the total number of cases for the year 1993. This figure is likely to be an underestimate because death certificates for England and Wales have not been available for the year 1993 and there may be a delay in obtaining final post mortem results in a small number of cases. However only approximately 6% of all definite and probable cases are identified from death certificates and it is unlikely that the total

TABLE 1

REFERRALS OF SUSPECT CASES TO THE CJD SURVEILLANCE UNIT

1 MAY 1990 - 30 APRIL 1994

316 SUSPECTED CASES REFERRED

REFERRED FROM	DEFINITE	PROBABLE	POSSIBLE	OTHER	GSS	UNCLASSIFIED
Neurologist	76	22	15	59	4	0
Pathologist	26	0	2	10	1	0
General Physician	10	2	1	6	0	0
Death Certificate	6	3	6	24	0	2
Psychiatrist	0	1	0	7	0	0
EEG Dept	5	1	2	8	0	1
Other	6	1	3	6	0	0
TOTAL	129	30	29	120	5	3

number of cases in 1993 will exceed the total number for 1992, even when outstanding information becomes available.

In Table 2, the numbers of cases of definite and probable CJD are listed by year since 1985 according to clinical subtype. This again confirms an increase in the number of cases of sporadic CJD but also shows that the increase in the total number of cases of CJD is influenced by a rise in the number of cases of iatrogenic CJD since 1990 and also an increase in the number of familial cases that have been identified in recent years.

Analysis of age-specific incidence rates pre- and post-1990 also shows a change with an increased frequency of CJD in those patients aged over 75 (Figures 2, 3 and 4). This is also illustrated in Figures 5 and 6 which show little change in the overall numbers of cases of sporadic CJD under the age of 75 and an increase in the numbers of cases over the age of 75 particularly in 1992 and 1993. Statistical analysis supports this impression. In England and Wales, for which there is epidemiological data extending back to 1979 there is strong evidence that the overall rate of CJD, taking account of the age and sex distribution of the population, varied between the different time periods (70-79, 80-84, 85-89 and 90-94) [$p < 0.001$]. Adjusting for age, sex and standard region, mortality rates were about 2¼ times higher in the period 1990-1994 than in the period 1970-1979. Excluding the period 1970-1979, where it is believed under-ascertainment of cases is likely to have occurred, there is still evidence that mortality rates differ between the different time periods ($p = 0.005$). Compared to the period 1980-1984 when ascertainment had been thought to be fairly complete, mortality was 13% lower in the period 1985-1989 (95% CI, 32% lower to 14% higher) but 32% higher in the period 1990-1994 (95% CI, 4-69% higher). When the oldest age group (75 and above) was excluded the differences between these time periods were of borderline statistical significance ($p = 0.08$), and the increase in the period 1990-1994 relative to the period 1980-1984 was reduced to 20% (95% CI, -8% to +55%). This finding is compatible with the hypothesis that at least some of the apparent increase in mortality rates in 1990-1994 may have been due to improved case ascertainment in the oldest age group (75 years and above).

TABLE 2

DEATHS FROM CREUTZFELDT-JAKOB DISEASE

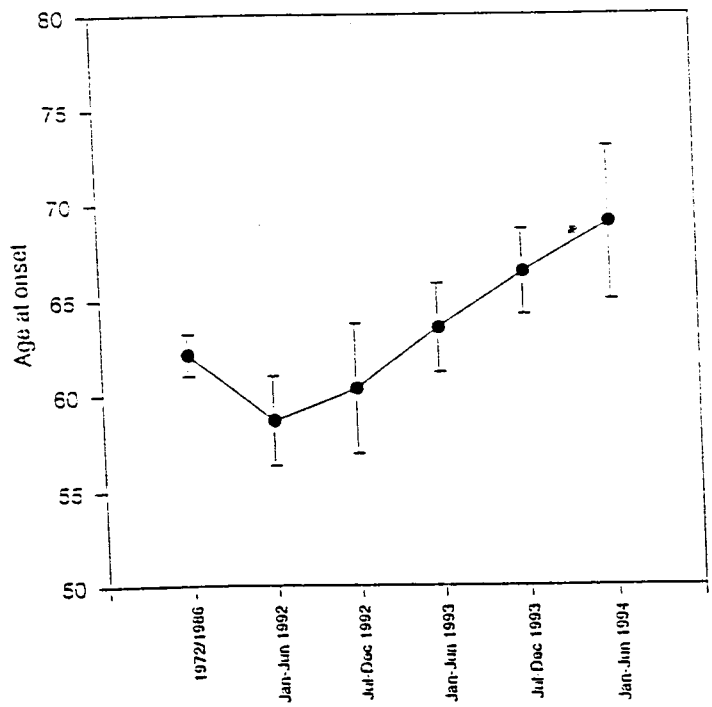
By Calendar Year (1985-1993)

Year	Sporadic	Iatrogenic	Familial	GSS
1985	26	1	1	0
1986	26	0	0	0
1987	23	0	0	1
1988	21	1	1	0
1989	28	1	1	0
1990	26	5	0	0
1991	32	1	3	0
1992	44	2	4	1
1993	34	3	2	1
1994 (up to April)	7	1	0	0

The geographical distribution of cases of sporadic CJD aged 75 years and over from 1980-1993 (Figure 7) shows that cases in this particular age group were discovered throughout the United Kingdom. It is of note that the clinical features, for example the duration of illness, in patients with CJD aged over 75 are indistinguishable from the younger age groups and also that only one of these elderly patients presented with a cerebellar syndrome. Genotype data is available on 14 cases aged 75 or over and of these 13 were methionine homozygotes at codon 129 and 1 a heterozygote.

It is also of interest that the mean age of onset of patients with CJD identified in the national surveillance programme in Italy has risen in each 6-month epoch since January 1992, and that the current mean age at onset of CJD is significantly higher than in epidemiological surveys carried out in Italy in 1972 and 1986 (Personal Communication, Professor M. Pocchiari)

MEAN AGE AT ONSET OF CREUTZFELDT-JAKOB DISEASE IN ITALY



(Data from the National CJD Surveillance Project in Italy, Istituto Superiore di Sanita, Viale Regina Elena 299, 00161 Roma, Italy, Professor M. Pocchiari).

BSE has not been identified in Italy and one explanation for the findings in Italy and the UK is that there is improved case ascertainment in older patients with CJD. Further evidence in relation to the identification of CJD in the elderly may

become available from the coordinated surveillance programme for CJD in the EC (vide infra).

The overall incidence of CJD is 30% higher in the years 1991, 1992 and 1993 in comparison to data available for the years 1980-1984. To put this finding in perspective, there has been a four-fold increase in the identified incidence of CJD in the USA between the years 1978-1988 (Davanipour Z, Smoak C, Bohr T, Sobel E, Liwnicz B. Rate of Creutzfeldt-Jakob disease in the USA. Neurology 1993; 43(4): A316). BSE has never been identified in the USA and it seems likely that much of this rise in incidence is due to improved case ascertainment. The increased incidence rate in the UK is probably related to a number of factors including an increase in the number of iatrogenic cases, an increase in the number of familial cases identified, and in particular an improvement in case ascertainment in patients aged over 75. However the incidence of CJD in the UK which rose in 1991 and 1992 has not risen further in 1993 as would have been expected in a common source epidemic, and the current incidence figures in the United Kingdom are comparable to those in other countries without BSE.

CLINICAL FEATURES

CJD may present with a range of clinical signs but there has been no overall change in the clinical features of CJD since 1980. For example, the duration of illness remains relatively constant and the proportion of patients presenting with a cerebellar syndrome remains low (Table 3). The theoretical importance of this type of presentation is that in iatrogenic CJD caused by human pituitary hormones and in kuru, the great majority of patients present with a progressive cerebellar ataxia. There is accumulating evidence that the clinical presentation in the human spongiform encephalopathies is influenced by the route of inoculation and that peripheral routes lead to a cerebellar syndrome while direct CNS inoculation, for example by neurosurgical cross-contamination or dura mater grafts, results in a clinical presentation indistinguishable from sporadic CJD in which there is progressive cortical dysfunction including dementia. If BSE caused disease in the human population this would involve transmission via a peripheral route and this might result in a cerebellar presentation rather than the classical clinical features of CJD.

TABLE 3 Patients with Progressive Cerebellar Presentations

Year of Death	Def	Prob	Poss	HGH/HGnH	%*
1990	7	2	0	5	12.5 (4/32)
1991	1	0	0	0	2.9 (1/35)
1992	3	0	2	2	6.1 (3/49)
1993	6	0	1	3	9.5 (4/42)

* "Cerebellar" cases as a percentage of sporadic cases (def, prob and poss, but excluding HgH/HGnH cases)

GEOGRAPHICAL DISTRIBUTION OF CASES

The geographical distribution of cases of CJD by place of residence at death for the period 1st May 1990 to 30th April 1994 is shown in Figure 8. Standardised mortality ratios (SMRs) for the standard regions are shown in Figure 9 for the period 1970-1984 and in Figure 10 for the period 1985-1994. The highest SMR in the earlier period was in the South East (127.0). This fell to 95.8 in the later period. A large change also occurred in the South West (a rise from 99.4 to 142.8). Scotland, included for the first time in the second period, also had a high SMR (139.8). When Scotland was excluded from the analysis there was no strong evidence that the geographical distribution of rates differed between the two periods ($p = 0.24$). Absolute mortality rates by county for the periods up to 1984 and after 1984 are shown in Figures 11 and 12 respectively. In the earlier period, 1970-1984, the highest rates (over 1 case/million/year) were observed in Dyfed and Oxfordshire (Figure 11). In the later period the rates in both these counties were lower (Figure 12). Between 1985 and 1994, 7 counties in England and Wales had rates above 1 case/million/year (Cornwall, Dorset, Avon, Powys, Berkshire, Northants and Cumbria). In Scotland high rates were observed in Borders, Central, Grampian and Lothian.

Space-time clustering of CJD

The method of Knox was used to look for evidence of clustering of cases of CJD in space and time (which might be interpreted as evidence for case-to-case transmission or as evidence of a common source outbreak). Two hundred and sixty-seven cases in Great Britain, identified since 1984, were included in the first analysis. Cases known to be iatrogenic or familial were excluded as was

one case from the Shetland Islands. When known, date of onset was used as the time point. When date of onset was unknown, it was set at 4 months prior to the date of death (4 months being the median duration from time of onset to time of death).

Table 4 Space-time clustering of dates and places of onset of 267 cases of Creutzfeldt-Jakob disease in Great Britain, 1985-1994: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other

Time [+] between dates of onset	Distance between places of residence at onset							
	< 5km		< 10 km		< 20 km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	4	4.5	8	8.5	21	21.0	53	53.1
1-3 months	7	6.4	15	12.2	25	30.1	68	76.1
3-6 months	8	9.9	15	18.7	43	46.2	124	116.7
6-12 months	18	19.3	34	36.6	93	90.3	227	228.0
1-2 years	31	33.3	63	63.2	141	155.9	373	393.6
2-3 years	19	27.8	40	52.8	127*	130.1	344	328.6
3-4 years	26	24.0	59*	45.5	126	112.2	296	283.4
4-5 years	30**	20.0	43	38.0	84	93.6	224	236.3

+ Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830
* p = 0.03
** p = 0.02

For most space-time combinations the observed number of pairs is very close to the number expected under the null hypothesis (no space-time clustering). Only two cells have excess observed pairs statistically significant at the 5% level. Fifty-nine pairs were observed to occur within 10km of each other with onset 3 to 4 years apart (about 46 such pairs were expected). This slight excess is largely explained by a cluster of 21 individuals (forming 27 pairs) in and around London. In addition, 30 pairs of cases occurred within 5km of each other with onsets 4 to 5 years apart (20 such pairs were expected). Again this excess is largely explained by two clusters in and around London (one of 6 individuals forming 9 pairs, the other of 5 individuals forming 6 pairs). Some of the

individuals in these clusters were the same individuals as in the cluster with onsets 3 to 4 years apart. Given the number of space-time combinations tested (32), we would not be surprised to find one or two cells significant at the 5% level in the absence of any clustering. The clusters observed may well have arisen through random variation.

An analysis of cases occurring in Great Britain over almost 25 years is presented in Table 5.

Table 5 Space-time clustering of dates and places of onset of 536 cases of Creutzfeldt-Jakob disease in Great Britain, 1970-1994: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other.

Time + between dates of onset	Distance between places of residence at onset							
	< 5km		< 10 km		< 20 km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	5	4.9	10	12.4	39	35.3	106	108.3
1-3 months	9	7.3	22	18.4	43	52.4	141	160.5
3-6 months	13	10.9	24	27.7	75	78.8	258	241.5
6-12 months	29	21.7	60	54.8	182*	156.0	493	478.3
1-2 years	40	40.8	98	103.3	300	294.1	887	901.5
2-3 years	26	38.1	80	96.5	278	274.6	904*	841.9
3-4 years	45	35.6	98	90.8	281	258.4	834	792.1
4-5 years	46*	33.8	85	85.5	219	243.4	755	746.1
5-6 years	41	32.5	100*	82.1	261	233.7	738	716.5
6-7 years	26	31.3	77	79.1	221	225.2	707	690.5
7-8 years	29	29.7	78	75.0	229	213.6	674	654.7
8-9 years	26	25.6	56	64.8	177	184.6	576	565.9
9-10 years	25	27.0	63	68.3	200	194.4	613	596.1
10-15 years	76	92.6	230	234.1	636	666.5	1973	2043.3
15-20 years	39	46.5	129	117.6	322	334.9	947	1026.7

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

* $0.01 < p < 0.05$

There is little evidence of space-time clustering of cases in this analysis. At 6-12 months apart there was an excess of pairs of cases at less than 20 km apart ($p = 0.02$). However, there was no evidence of any excess either at a slightly shorter time interval (3-6 months) or at a slightly longer time interval (1-2 years). There was also an excess of pairs of cases occurring 2-3 years apart and within 50km of each other ($p = 0.02$). At closer distances, however, there was no excess of pairs. At 4-5 years apart, there was an excess of pairs within 5 km of each other ($p = 0.03$). More pairs than expected were also observed within 5 km of each other at both a slightly shorter (3-4 years) and a slightly longer (5-6 years) time interval, although neither of these excesses were statistically significant on their own. Combining these three cells of the table together, to look at pairs occurring 3 to 6 years apart within 5km of each other, reveals 132 observed pairs against 102.1 expected ($p = 0.003$). The largest cluster among these pairs consisted of 24 individuals (forming 61 pairs) with onset in the greater London area between February 1973 and May 1993. At 5-6 years interval there was also an excess of pairs of cases within 10 km of each other ($p = 0.03$). The finding of several small excesses of pairs should not be interpreted as strong evidence of space-time clustering. Fifteen different time intervals were considered initially, together with 4 different distances. In the absence of any real space-time clustering one might reasonably expect to observe several statistically significant excesses.

This data does not suggest any major change in the geographical distribution of cases of CJD since the advent of BSE. In considering the observed clusters in London, it should be noted that a relatively high incidence of CJD was discovered in the Paris region in the study of CJD in France 1970-1984 and in Santiago, Chile 1970-1983, possibly attributable to increased ascertainment of cases in urban areas.

CASE CONTROL STUDY OF CJD

In addition to the descriptive epidemiological and clinical analyses, a case-control study of CJD has been carried out in the UK since May 1990. The methodology of this study parallels the previous case-control study of CJD carried out between 1980-1984 in England and Wales by Professor WB Matthews. Relatives of patients with suspect CJD are interviewed using a standard questionnaire, adapted from the previous study, which includes a

wide range of questions relating to putative risk factors for CJD including occupational history and dietary history. For each index case a control is identified in the same hospital and is matched for sex and age $\pm$ 4 years. Cases with diseases which might be confused clinically with CJD are excluded. Where possible, a relative of the same degree is interviewed using the standard questionnaire and if this is not possible, the control is interviewed directly. Since May 1990 a relative of the control has been available in 57% and the control has been interviewed directly in 43%.

109 cases of sporadic CJD have been included in the case-control study out of 139 cases identified since May 1990. Exclusion from the case-control study in the 30 remaining cases has been due to a variety of reasons, the most common being that the case was identified only after death.

There are major methodological problems with the case-control study. Most importantly, the relatives of suspect cases of CJD are frequently fully aware of the hypotheses under investigation, for example the theoretical risk of dietary exposure to bovine products, and this has the potential to introduce major bias.

Occupational History and Risk of CJD

Cases and controls were compared with regard to their own and their spouse's occupational history. Table 6 presents the results of this comparison.

One case had worked in a school animal laboratory (pre-1985). No other cases, nor controls, nor their spouses had ever worked in animal, pharmaceutical or other research laboratories. Slightly more controls than cases had worked in or been married to someone who worked in the medical professions or as a farmer or "vet". Slightly more cases than controls had worked as or been married to butchers (10 versus 7, $p = 0.45$). The same was true for other occupations involving animal products (14 versus 11, $p > 0.20$). Restricting attention to occupations post-85 produced no stronger evidence of any association between occupation and risk of CJD. Four cases compared with 2 control had contact with the medical profession. Three cases versus 2 controls had contact with farming/veterinary medicine, 2 cases versus 1 control had contact with butchering etc., while 2 cases and 2 controls had contact with occupations involving animal products. None of these data provide any evidence of a link between occupational exposure to animals/animal products and risk of CJD.

Table 6 Results of a comparison of 110 sporadic cases of CJD with their matched controls with regard to their lifetime occupational history and that of their spouse

Occupation	Exposure	Number (%) of cases	Number (%) of controls
Medical/paramedical/ nursing/dentistry	Subject	7 (6)	11 (10)
	Spouse	4 (4)	3 (3)
	Neither	99 (90)	96 (87)
Animal laboratory	Subject	1 (1)	0 (0)
	Spouse	0 (0)	0 (0)
	Neither	109 (99)	110(100)
Farmer/Veterinary Surgeon	Subject	7 (6)	8 (7)
	Spouse	1 (1)	2 (2)
	Neither	102 (93)	100 (91)
Butcher/abattoir worker/other occupation with direct contact with animals/carcasses	Subject	5 (5)	5 (5)
	Spouse	5 (5)	2 (2)
	Neither	99 (90)	103 (94)
Occupation involving animal products	Subject	10 (9)	9 (8)
	Spouse	4 (4)	2 (2)
	Neither	96 (87)	99 (90)

The presentation of data related to specific occupations can lead to misunderstanding. Table 7 lists the lifetime occupations in 50 recent consecutive cases of definite and probable sporadic CJD in order to demonstrate the broad range of past or present occupations in patients with CJD.

Table 7 Lifetime occupations in 50 cases of definite and probable sporadic CJD.

Accountant
Accountant
Air Hostess
Air Raid Warden
Ammunition Worker
Apprentice Optician
Army Corporal
Army Officer
Bakery
Bank Clerkess
Bellboy
Biscuit Factory
Bomb Disposal in War
Bomb Disposal (Army)
Book-keeper
Builder
Bus Driver
Butcher
Canteen Worker
Caretaker
Carpenter
Cashier
Child Minder
Children/Elderly Persons Home
Civil Servant
Civil Servant
Cleaner
Cleaner and Dyer
Clerical Work
Clerical Work
Clerical Work
Clerk
Clothing Industry
Colonial Service
Contractor (Metal Storage Units)
Contracts Manager
Cook
Cooking Hams
Crofter
Diplomat
Domestic
Engineer
Engineer
Estate Agent
Factory Packer
Factory Worker
Factory Worker
Farmer
Fat Melting Business
Fireman
Fireman
Governess
GP
Greengrocer
Grocer
Guest House
Home help
Hotel Receptionist
Housewife
Housewife
Housework
Journalist
Labourer
Laundry Assistant
Lecturer
Machine Operator
Machine Tool Engineer
Machinist
Making Tank Components
Managing Director
Managing Director
Medical Secretary
Milkman
Milkman
Miner
Jehovah's Witness Minister
Navy - apprentice
Packer
Packer for dairy firms
Pattern technician
Post Office Clerkess
Priest
Private Secretary
Process Worker - Metalworks
Processing work (veg)
Radio Wirer
RAF
Receptionist
Sales
Sales Rep
School Cook
School Dinner Lady
School Teacher
Secretary
Shop Assistant
Shop Assistant
Shop Assistant
Shop Assistant
Shop Assistant
Shop Assistant
Shop Assistant (Bridal)
Shop Assistant (Conf/Pharm)
Show Card Assembler
Sweet Packer
Sweet Packer
Telecom Traffic Superintendent
Telephonist
Timekeeper
Toy Maker
Train Driver
Trainee Nurse
Transport Depot Manager
Tutor
Typist
Typist
Upholsterer
Voluntary Services
Waitress
Warehouseman
Waterboard
Weaver
Weaver
Welder
Window Cleaner
Wire Netting Manufacturer
Woodyard Worker

Dietary History and Risk of CJD

One hundred and nine cases of Creutzfeldt-Jakob disease identified between May 1990 and April 1994 were compared with age- and sex-matched controls with regard to lifetime history of eating of meat or meat products. Consumption was recorded as follows: never, less than once per year, more than once per year but less than once per month, more than once per month but less than once per week, once per week or more, eaten but frequency unknown. For all cases and for 62 (57%) controls, information on dietary history was obtained from a relative. For the remaining 47 controls, information was obtained from the control directly. In addition to collecting information on lifetime dietary history, dietary history since 1985 was also recorded for some products. This information was available for 81 (74%) of case-control pairs.

The analyses were performed using the computer package EGRET, using exact methods or conditional logistic regression. All odds ratio estimates take account of the individual matching.

The findings concerning dietary history are particularly difficult to interpret for two reasons.

1. First, in the absence of any systematic bias in the responses between cases and controls to questions about diet, there is likely to be substantial misclassification of exposure. While it may be quite easy to respond accurately to questions concerning diet and frequency for items that one never eats, or eats every day, it is more difficult to respond accurately for items that one eats infrequently. The problem acquires another degree of magnitude when the question is not about personal dietary habits but those of a relative. In the absence of any systematic bias in responses this misclassification will tend to hide any associations which exist between dietary items and risk of CJD.

2. Substantial potential for response bias exists. BSE has received much exposure in the press, much of it of the sensational variety. There can be few people who have not heard of "mad cow disease". There are also likely to be few people who are not aware of the hypothesis that eating beef/cow products may lead to disease in humans. Relatives of cases of CJD aware of such hypotheses may overestimate the frequency with which the case ate various meats/animal products compared with

controls/relatives of controls for whom the questions bear no special significance. This type of misclassification will tend to overestimate any association which exists between diet and risk of CJD or may even create an apparent association where none actually exists.

The results of the comparison of 109 case-control pairs with regard to lifetime consumption of different types of meat (never versus ever) is shown in Table 8. Evidence of trends in consumption was also sought by fitting the consumption categories described above (coded 1, 2, 3, 4 and 5) as a continuous variable (Table 8). It should be noted that the two p-values for each type of meat are not independent of each other.

Pork, poultry and fish were consumed by almost all cases and controls. There was no evidence of any trend towards cases consuming these items more often than controls. Similar results were obtained when attention was restricted to those case-control pairs for whom control data were obtained from a relative.

Lamb and beef were also very widely consumed. Cases were reported to consume both of these meats more often than controls (test for trend; lamb, $p = 0.01$; beef, $p = 0.12$). For lamb the association was unchanged when attention was restricted to those case-control pairs with data from relatives. The statistical evidence of an association between beef eating and risk of CJD was stronger when attention was restricted to those pairs for whom control data came from a relative ($p = 0.05$).

Consumption of venison and veal was much less widespread among both cases and controls. For both of these meats there was evidence of a trend with increasing frequency of consumption being associated with increasing risk of CJD. These associations were largely unchanged when attention was restricted to pairs with data obtained from relatives.

Table 8 Results of a comparison between 109 cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls with regard to lifetime history of eating different types of meat

Type of meat	Cons-umed	Number of cases (%)	Number of controls (%)	Odds ratio (OR)	95% Confidence intervals (c.i.)	p-value (OR = 1)	p-value (trend)
Lamb	No	1 (1)	7 (7)	1.0	-	0.07	0.01
	Yes	108 (99)	100 (93)	7.00	(0.90,315.3)		
Pork	No	0 (0)	2 (2)	1.0		0.50	0.24
	Yes	109(100)	105 (98)	∞.	(0.19,∞)		
Beef	No	0 (0)	1 (1)	1.0		1.00	0.12
	Yes	109(100)	106 (99)	∞.	(0.13,∞)		
Venison	No	79 (75)	93 (85)	1.0		0.05	0.03
	Yes	27 (25)	16 (15)	2.10	(0.99,4.46)		
Veal	No	74 (70)	90 (83)	1.0		0.01	0.001
	Yes	32 (30)	18 (17)	2.56	(1.18,5.52)		
Poultry	No	0 (0)	0 (0)	-		1.00	0.66
	Yes	107(100)	109(100)	-			
Fish	No	1 (1)	0 (0)	1.0		1.00	0.49
	Yes	107 (99)	106(100)	0.00	(0.00,39.0)		

In order to investigate further the trends observed (for lamb, beef, venison and veal), the data were regrouped into the following categories:

- lamb and beef; less than monthly, at least monthly, weekly;

- venison and veal; never, less than yearly, yearly.

(Regrouping was performed because with the original five categories used the data were too sparse).

Tables 9A and 9B present the results of an analysis of these data. There is some evidence that risk of CJD increases with increasing frequency of lamb eating ($p = 0.02$). The evidence for such an association between beef eating and risk of CJD is weaker ($p = 0.14$). When only controls for whom a relative was interviewed are included, this evidence becomes a little stronger ($p = 0.08$).

Table 9A Results of an analysis of trends in consumption of lamb and beef, between cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Lamb	< monthly	22 (21)	38 (36)	1.0	-	0.02
	monthly	62 (58)	53 (50)	1.95	(0.99,3.81)	
	weekly	23 (22)	15 (14)	2.45	(1.03,5.85)	
Beef	< monthly	6 (6)	14 (13)	1.0	-	0.14
	monthly	46 (43)	45 (42)	2.51	(0.85,7.37)	
	weekly	55 (51)	48 (45)	2.68	(0.93,7.75)	
Beef*	< monthly	2 (3)	7 (12)	1.0	-	0.08
	monthly	25 (42)	28 (47)	2.83	(0.54,14.9)	
	weekly	33 (55)	25 (42)	3.93	(0.79,19.6)	

*Results from analysis including only those case-control pairs for which a relative of the control was interviewed.

Just as in last year's report, in which an apparent association between risk of CJD and consumption of 'puddings' was identified, the current statistical analysis has revealed two dietary factors, veal and venison, which are associated with an apparent major increase in the risk of CJD. It is of note that in the current analysis, 'pudding' consumption is no longer associated with an increased risk of CJD.

TABLE 9B Results of an analysis of trends in consumption of venison and veal between cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Venison	never	79 (75)	93 (85)	1.0	-	0.02
	< yearly	16 (15)	14 (13)	1.30	(0.55,3.06)	
	yearly	10 (10)	2 (2)	9.27	(1.17,73.4)	
Veal	never	74 (70)	90 (83)	1.0	-	0.001
	< yearly	17 (16)	14 (13)	1.35	(0.55,3.32)	
	yearly	15 (14)	4 (4)	13.32	(1.74,102.0)	

There is strong evidence of an association between "regular" veal eating and risk of CJD ($p = 0.01$). Individuals reported to eat veal on average at least once a year appear to be at 13 times the risk of individuals who have never eaten veal. There is, however, a very wide confidence interval around this estimate. There is no strong evidence that eating veal less than once per year is associated with increased risk of CJD ($p = 0.51$). The association between venison eating and risk of CJD shows a similar pattern, with regular venison eating associated with a 9 fold increase in risk of CJD ($p = 0.04$).

In order to examine for the possibility of recall bias in index cases in comparison with control cases, the frequency of veal consumption was analysed in cases referred to the Unit as suspect CJD in which the final diagnosis was judged to be not CJD. This group includes cases in which the diagnosis of CJD was refuted after histological examination of the brain (58% of "not" cases with control data), and cases in which CJD was judged to be unlikely on clinical grounds, for example a significant proportion of these cases recovered and/or

are still alive. The "not CJD" cases are a particularly appropriate group to analyse in relation to recall bias because the respondents were aware of the possibility of CJD at the time of the interview and were thus subject to the same potential biases as the respondents in cases later judged to have CJD.

Table 10 shows the frequency of veal consumption in cases of CJD and suspect cases of CJD subsequently classified as "not CJD".

TABLE 10 Analysis of frequency of veal consumption in 109 cases of sporadic of CJD and in 54 cases judged to be "not CJD"

	Consumed	Percentage of CJD Cases	Percentage of "Not-CJD" Cases
Veal	No	70	69
	Yes	30	31
Veal	Never	70	69
	< Yearly	16	18
	Yearly	14	13

Thus, the reported veal eating habits of confirmed CJD cases appear virtually identical to suspect cases later judged not to have the disease. This provides good circumstantial evidence to support the hypothesis that the apparent association between veal consumption and CJD is due to recall bias. Analysis of other apparent dietary risk factors for CJD, including venison, has provided similar evidence of recall bias.

In addition to data on frequency of eating different types of meat, data were also collected on frequency of eating other animal "products". Table 11 presents a comparison of cases and controls with regard to lifetime consumption of these products.

Table 11 Results of a comparison between 109 cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls with regard to lifetime history of eating various animal products.

Type of product	Cons-umed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (OR = 1)	p-value (trend)
Sausage	No	0 (0)	3 (3)	1.0	-	0.25	0.87
	Yes	106(100)	105 (97)	∞	(0.41,∞)		
Tripe	No	77 (71)	79 (75)	1.0	-	0.41	0.64
	Yes	32 (29)	27 (25)	1.31	(0.68,2.52)		
Liver	No	14 (13)	16 (15)	1.0	-	0.56	0.47
	Yes	95 (87)	91 (85)	1.25	(0.59,2.67)		
Kidney	No	35 (32)	52 (48)	1.0	-	0.02	0.04
	Yes	74 (68)	56 (52)	2.00	(1.12,3.58)		
Sweet-breads	No	96 (90)	101 (94)	1.0	-	0.28	0.42
	Yes	11 (10)	7 (6)	1.80	(0.60,5.37)		
Tongue	No	49 (46)	61 (56)	1.0	-	0.08	0.89
	Yes	58 (54)	48 (44)	1.73	(0.92,3.27)		
Brains	No	91 (84)	103 (94)	1.0	-	0.01	0.06
	Yes	17 (16)	6 (6)	3.20	(1.17,8.74)		
Trotters	No	88 (81)	92 (86)	1.0	-	0.37	0.08
	Yes	20 (19)	15 (14)	1.39	(0.68,2.83)		
Puddings	No	47 (44)	54 (50)	1.0	-	0.34	0.95
	Yes	60 (56)	55 (50)	1.35	(0.72,2.53)		
Haggis	No	73 (68)	81 (74)	1.0	-	1.00	0.82
	Yes	34 (32)	28 (26)	1.40	(0.72,2.72)		
Heart	No	78 (73)	81 (77)	1.0	-	0.32	0.60
	Yes	29 (27)	24 (23)	1.31	(0.72,2.72)		

Almost all cases and controls were reported to have eaten sausages at some time and there was no evidence of any dose-response relationship. Slightly more cases than controls were reported to have eaten haggis and heart, but these differences were not statistically significant, nor was there any evidence of a dose-response relationship. More cases than controls were reported to have eaten tongue, but again the evidence against this being a chance finding was weak ($p = 0.08$) and there was no evidence of a dose-response effect. (When only case-control pairs using data from relatives were analysed the odds ratio fell to 1.36).

Slightly more cases than controls were reported to have eaten tripe, liver, sweetbreads, trotters and puddings. None of these differences were statistically significant. There was some evidence of dose-response relationships involving trotters. Substantially more cases than controls were reported to have eaten kidneys and brains and both these associations showed some evidence of a dose-response relationship.

Table 12 presents a more detailed analysis of the associations between lifetime consumption of trotters, kidneys and brains, and risk of CJD. Consumption was regrouped into 3 categories: never; less than once per year; once per year or more. Eating kidneys and brains were both associated with statistically significant trends, "regular" eating of either (once per year or more) being associated with a two- to three-fold increase in risk. The trend in the odds ratios was apparent for kidneys but was not so evident for brains. Restricting attention to the subset of case-control pairs with exposure data obtained from relatives did not alter greatly the results - the "trend" was unchanged for brains and was slightly stronger for kidneys. The evidence for an association between the eating of trotters and risk of CJD was more equivocal. There was no clear trend in the estimates of the odds ratios, nor was there strong statistical evidence of a trend ($p = 0.09$). When attention was restricted to pairs with data obtained from relatives, there was stronger evidence of a trend ($p = 0.003$).

Table 12 Results of analysis of trends in lifetime consumption of kidneys, brains and trotters between cases of Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Kidneys	never	35 (33)	52 (50)	1.0	-	0.01
	< yearly	15 (14)	14 (13)	1.71	(0.73,4.00)	
	yearly	56 (53)	39 (37)	2.28	(1.21,4.29)	
Brains	never	91 (85)	103 (94)	1.0	-	0.03
	< yearly	11 (10)	4 (4)	3.00	(0.94,9.62)	
	yearly	5 (5)	2 (2)	3.00	(0.56,16.2)	
Trotters	never	88 (83)	92 (88)	1.0	-	0.09
	< yearly	9 (8)	11 (10)	0.88	(0.36,2.15)	
	yearly	9 (8)	2 (2)	7.89	(0.99,63.2)	

It is likely that many of the dietary exposures considered are associated in the population. For example, one might expect that individuals who eat a particular type of offal are more likely to eat other types than individuals who do not. Thus there is potential for major confounding of associations between dietary exposure and risk of CJD. In order to overcome this problem, conditional logistic regression analysis was used to model simultaneously the association between different exposures and risk of CJD. Dietary items examined in this way were: lamb, beef, venison, veal, kidney, brains and trotters. It was found that when veal was included in the model with another exposure, the association between veal and CJD remained statistically significant ($p < 0.05$ for all other exposures), while the other exposures ceased to be statistically significant ($p > 0.05$).

Data on consumption of animal products post-1985 were available for 81 case-control pairs and are summarised in Table 13. There was no evidence of any association between consumption of tripe, brains or puddings and risk of CJD. More cases than controls were reported to have eaten sausage, liver, sweetbreads, tongue, trotters, haggis and heart. However, none of these differences were statistically significant. Moreover, for none of these products was there any statistical evidence of a dose-response relationship. Cases were more likely than controls to have eaten kidneys and there was some evidence for a dose-response relationship ($p = 0.04$). Kidney consumption (post 1985) was then reclassified into 3 categories (Table 14). "Irregular" consumption (less than yearly) was associated with almost a doubling of risk of CJD while more regular consumption was associated with an almost 2½-fold increase in risk.

Table 13 Results of a comparison between 81 cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls with regard to history since 1985 of eating various animal products

Type of product	Cons-umed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (OR = 1)	p-value (trend)
Sausage	No	2 (3)	6 (8)	1.0	-	0.29	0.88
	Yes	78 (98)	74 (93)	3.00	(0.54,30.4)		
Tripe	No	70 (86)	67 (85)	1.0	-	1.00	0.33
	Yes	11 (14)	12 (15)	0.92	(0.37,2.27)		
Liver	No	13 (16)	18 (23)	1.0	-	0.35	0.46
	Yes	68 (84)	61 (77)	1.55	(0.68,3.65)		
Kidney	No	30 (37)	48 (60)	1.0	-	0.01	0.04
	Yes	51 (63)	32 (40)	2.29	(1.19,4.64)		
Sweet-breads	No	76 (94)	78 (98)	1.0	-	0.45	0.40
	Yes	5 (6)	2 (3)	2.50	(0.41,26.3)		
Tongue	No	42 (52)	52 (64)	1.0	-	0.12	0.88
	Yes	39 (48)	29 (36)	1.83	(0.87,4.06)		
Brains	No	78 (98)	79 (98)	1.0	-	1.00	0.43
	Yes	2 (3)	2 (2)	1.00	(0.07,13.8)		
Trotters	No	75 (93)	79 (98)	1.0	-	0.29	0.17
	Yes	6 (7)	2 (2)	3.00	(0.54,30.4)		
Puddings	No	43 (54)	44 (54)	1.0	-	1.00	0.75
	Yes	37 (46)	37 (46)	1.00	(0.46,2.20)		
Haggis	No	61 (75)	67 (83)	1.0	-	0.33	0.61
	Yes	20 (25)	14 (17)	1.60	(0.68,3.94)		
Heart	No	69 (86)	74 (93)	1.0	-	0.42	0.76
	Yes	11 (14)	6 (8)	1.80	(0.54,6.84)		

Table 14 Results of analysis of trends in consumption of kidneys (post 1985) between cases of sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Kidneys	never	30 (38)	48 (61)	1.0	-	0.01
	< yearly	9 (11)	6 (8)	1.92	(0.66,5.60)	
	yearly	41 (51)	25 (32)	2.42	(1.21,4.85)	

In conclusion, an analysis of dietary histories revealed statistical associations between various meats/animal products and increased risk of CJD. When some account was taken of possible confounding, the association between veal eating and risk of CJD emerged as the strongest of these associations statistically.

The potential importance of clinical presentation and genotype in relation to assessing potential risk factors for CJD have been commented on in the previous report and earlier in this report. In relation to individuals who had consumed veal none of these patients presented with a cerebellar syndrome and the genotype distribution at codon 129 of the PrP gene is available in 20 cases with 17 methionine homozygotes, 2 heterozygotes and one valine homozygote. This distribution parallels the overall distribution of genotypes in all cases of sporadic CJD. The average age of individuals who had consumed veal was 64 and the geographical distribution of veal eaters is shown in Figure 13 and demonstrates a wide distribution of such cases with no aggregation in a specific locality.

It is also important to stress that the questions relating to dietary history are asked from a relative about a patient's lifetime consumption of various products. It is not possible to define the species source of specific types of animal product, for example kidney or brain, and it is of note that in last year's study the major dietary association with CJD related to the consumption of puddings, an association which is now no longer significant.

In summary, the analysis of the dietary case-control study demonstrates a strong association between a lifetime history of veal consumption and the risk

of developing Creutzfeldt-Jakob disease. However this result may well be due to recall bias and analysis of clinical and molecular biological features does not provide supportive evidence for the hypothesis that veal eating is a risk factor for CJD.

MOLECULAR BIOLOGY

A total of 120 samples of DNA from patients with CJD have been analysed prospectively either by the Prion Protein Research Group at St. Mary's Hospital in London or the Centre for Genome Research in Edinburgh. Nine mutations of the prion protein gene have been identified providing a figure for the overall genetic incidence of CJD of 13.4%. This represents an approximate doubling in the identification of cases presumed to be familial CJD in relation to the previous study in 1980-1984 and this indicates that a significant proportion of familial/genetic cases of CJD may only be identified through molecular biological techniques.

The genotype at codon 129 of the Open Reading Frame of the prion protein gene has been analysed in 117 cases of sporadic CJD (Figure 14). There is a variable genotype at this genetic locus in the normal population and, in contrast to mutations of the PrP gene in familial cases described above, this polymorphism of the PrP gene is not directly linked to an increased risk of sporadic CJD. Recent evidence does however suggest that the genotype at codon 129 of the PrP gene may influence susceptibility to both sporadic and iatrogenic CJD. Homozygosity at this locus is more common in CJD than in the general population, with an excess of methionine homozygotes in sporadic CJD and in cases of iatrogenic CJD due to central contamination. In iatrogenic CJD caused by pituitary hormone treatment, there is again an excess of homozygotes but in this group there is a relative excess of valine homozygotes.

In the study of CJD in the UK the distribution of genotypes at codon 129 in sporadic CJD confirms a marked excess of homozygous genotypes at this locus with particular reference to methionine homozygosity. This confirms the findings from previous studies of sporadic CJD. The distribution of genotypes at codon 129 in cases classified as "possible" or "other" are not significantly different from the normal population providing some support for the accuracy of the diagnostic criteria.

If BSE were to cause disease in the human population the distribution of genotypes at codon 129 might change to become more similar to the distribution of genotypes in the pituitary hormone related cases. The relative proportion of genotypes at codon 129 have therefore been analysed in each year of the study (Table 15) and there has been no overall change.

TABLE 15 Genetic data in sporadic CJD

Year	MM	MV	VV	MV + VV/Total
1990	8	0	1	11.1%
1991	10	2	0	16.7%
1992	19	2	3	20.8%
1993	16	2	1	15.8%

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

National surveillance projects for CJD have been established in France, Germany, Italy, The Netherlands and Slovakia. A grant from the European Community was awarded in 1993 in order to coordinate these surveillance projects which now share common diagnostic criteria, methodologies and case-control questionnaire.

Provisional figures for the incidence of CJD in participating countries was published in a letter to the Lancet earlier this year (Appendix 1) and demonstrated no significant difference in the incidence of CJD between the various countries. BSE has not been identified in Italy or the Netherlands and has a very low incidence in both France and Germany in contrast to the United Kingdom. This provides good evidence that up to 1993 there had been no significant change in the incidence of CJD that could be attributable to BSE. (It should be noted that the incidence figures for the United Kingdom were based on data available in February 1994 and that the analysis was based on numbers of incident cases and not deaths per annum).

The coordination of surveillance projects for CJD in the European Community is potentially of great importance in assessing any epidemiological change in CJD in the United Kingdom. In particular, the case-control study will provide

important comparative evidence on the risk factors for CJD and may allow any positive findings from any individual country to be put in context. For example, as part of the EC project, a meta-analysis of previous case-control studies of CJD has recently been completed, which includes data from case-control studies in the USA (1970-1981), Japan (1975-1977) and England & Wales (1980-1984). In the study in the USA, a range of foodstuffs were associated with an increased risk of CJD, including liver consumption which was associated with an apparent six-fold increase in the risk of CJD. By comparing the data from 3 studies in relation to this particular dietary factor, the risk of liver consumption became non-significant with an odds ratio of 1.2 (Personal Communication, Professor A. Hofman, Erasmus University, Rotterdam).

CJD IN AN ADOLESCENT

There has been a great deal of publicity in relation to one specific case of suspect CJD which was identified in 1993. It is the policy of the CJD Surveillance Unit not to comment on any individual case for reasons of confidentiality. On the other hand, it is clearly essential that details on specific cases of concern should become public knowledge and in the past this has resulted in published case-reports on specific cases, for example two dairy farmers with CJD who had had BSE in their herds. A case-report relating to the adolescent mentioned above is in Appendix 2.

CONCLUSIONS

The national surveillance programme for CJD in the United Kingdom was initiated in May 1990. The information provided in this report continues to provide evidence of a high level of case ascertainment and that detailed clinical and epidemiological information has been obtained in the great majority of cases. A high post mortem rate has been maintained throughout the period of the study. The success of the project continues to depend on an extraordinary level of cooperation 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.

Over a period of almost 25 years, the number of cases of CJD identified annually has increased. There was some increase during the first part of the period (1970-1979) followed by a period where the number of cases identified

remained fairly stable (1980-1989) followed by a further increase in the last few years. Since 1990, the crude mortality rate in England and Wales has been 0.64/million/annum while in Scotland it has been slightly higher (0.97/million/annum) and in Northern Ireland lower (0.47/million/annum). It is impossible to say with certainty to what extent these changes reflect an improvement in case ascertainment and to what extent, if any, changes in incidence. It is however clear that a number of factors have contributed to the rise in incidence including an increased number of iatrogenic cases, increased identification of familial cases and in particular an increase in identification of cases of CJD in the elderly. This is most likely to be due to improved case ascertainment in this particular age group.

There is no strong evidence of changes in the geographical distribution of CJD between the periods 1970-1984 (pre-BSE) and 1985-1994 (post-BSE). Previous analysis found no convincing evidence of space-time clustering during the earlier period. Nor did we find any convincing evidence of space-time clustering in the later period (1985-1994).

Analysis of occupational histories has revealed no evidence that any of the occupations considered on biological grounds as theoretically carrying a risk of CJD were actually associated with an increased risk of CJD. Occupational histories are probably subject to less bias than dietary histories.

Analysis of dietary histories revealed statistical associations between various meats/animal products and increased risk of CJD. The strongest of these associations statistically was with veal eating. Given the amount of publicity that BSE has received recall bias must be considered as a potential explanation for this association. Indeed, it might be argued that it is highly unlikely that such bias has not occurred to at least some extent. Circumstantial evidence to support recall bias as the explanation comes from an examination of dietary histories of suspected cases of CJD later judged not to have the disease. These patients had similar histories with regard to veal eating as confirmed cases. However, while it is entirely plausible that recall bias is the explanation for the observed association, and there is good circumstantial evidence to support such an explanation, we cannot discount absolutely the possibility of a link between veal eating and a risk of CJD.

Evidence from the combined study of CJD in the EC has demonstrated no difference in the incidence of CJD in countries with or without BSE. This project promises to provide extremely important comparative information in assessing any change in the epidemiological parameters of CJD that may be identified in the United Kingdom.

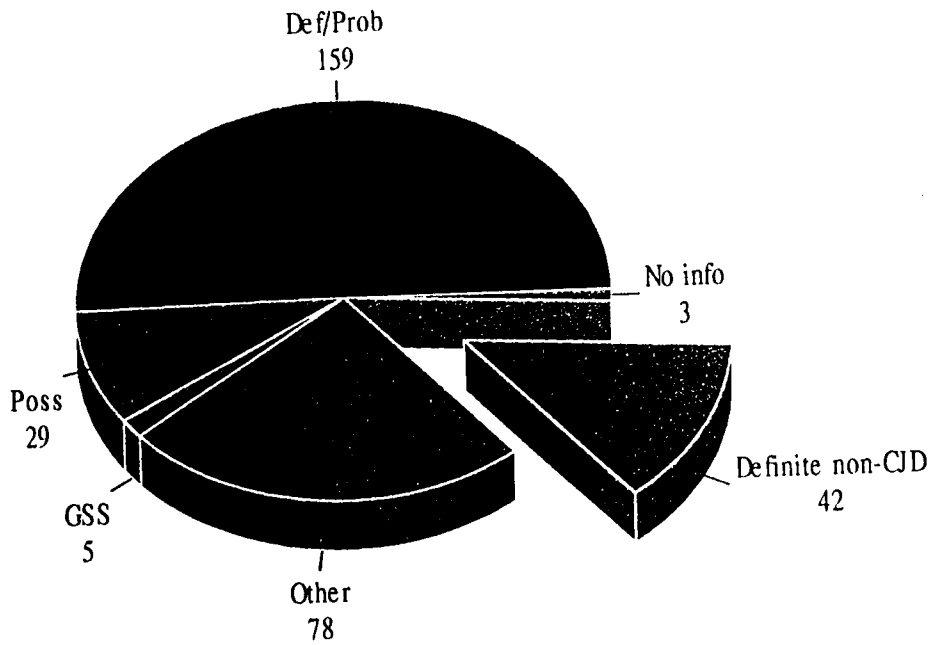
The overall conclusion of the study is that there is no conclusive evidence of any change in CJD that can be attributable to BSE. These negative findings should be interpreted with caution given the potentially long incubation period of CJD. If, for example, exposure to cattle or cattle products carries an increased risk of CJD since 1985, it may still be too soon to see evidence of that increased risk.

FIGURES

FIGURE 1

Referrals to CJD Unit

Final classification (1 May 1990 - 30 April 1994)



Definite non-CJD	
Alzheimer's disease (ATD)	18
ATD + MID	5
ATD + LBD	1
Multi-infarct (MID)	5
Hypoxia	2
Lewy body (LBD)	1
Motor neurone disease	2

1 each of Pick's disease, metastatic carcinoma,encephalomyelitis, cerebellar degeneration, Steele-Richardson syndrome, Multi-system atrophy, Cortico-basal degeneration & "myelinopathy"

FIGURE 2

CREUTZFELDT-JAKOB DISEASE - SPORADIC CASES

AGE-SPECIFIC INCIDENCE RATES FOR AGE AT DEATH

1980-1984

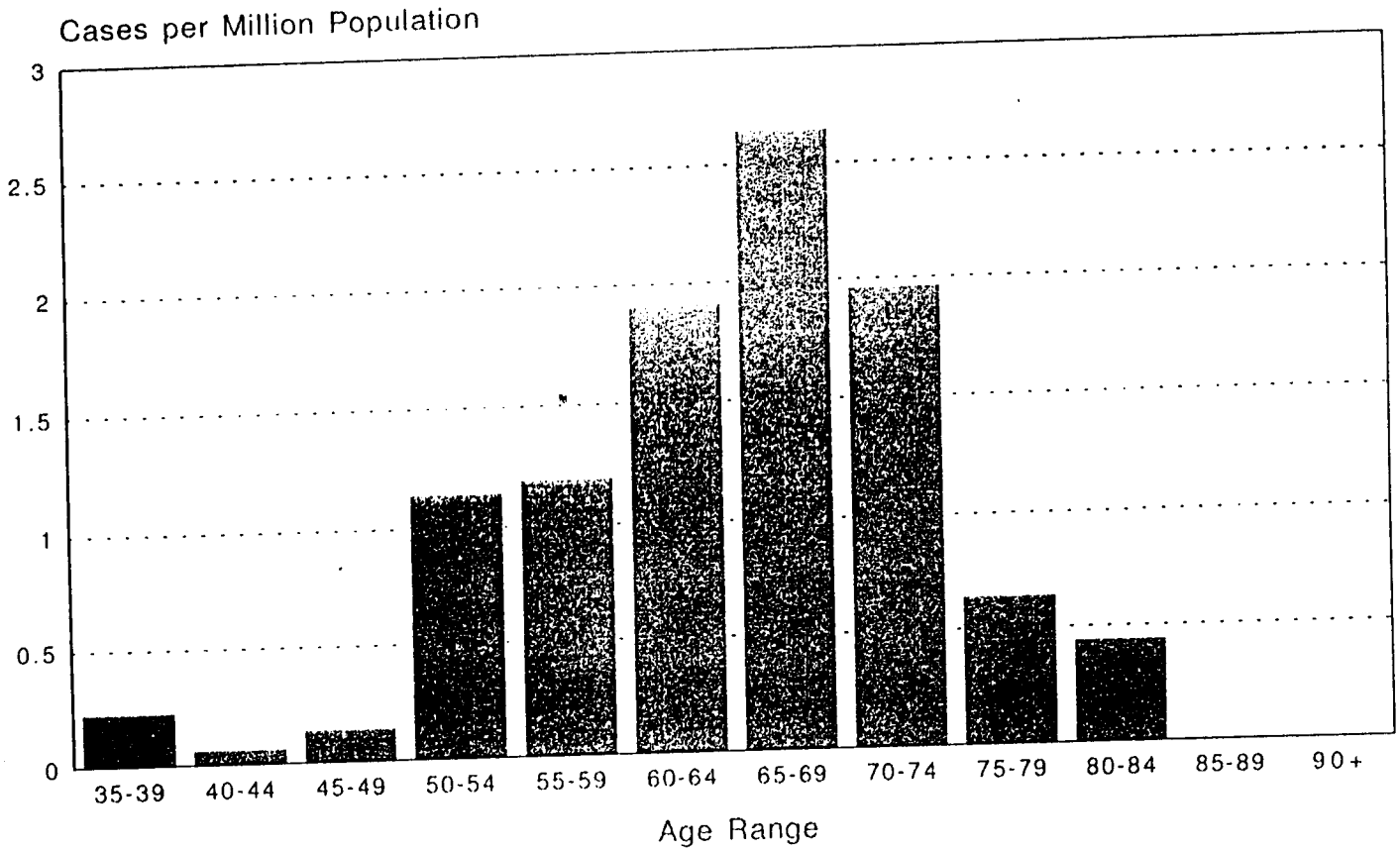


FIGURE 3

CREUTZFELDT-JAKOB DISEASE - SPORADIC CASES

AGE-SPECIFIC INCIDENCE RATES FOR AGE AT DEATH

1985-1989

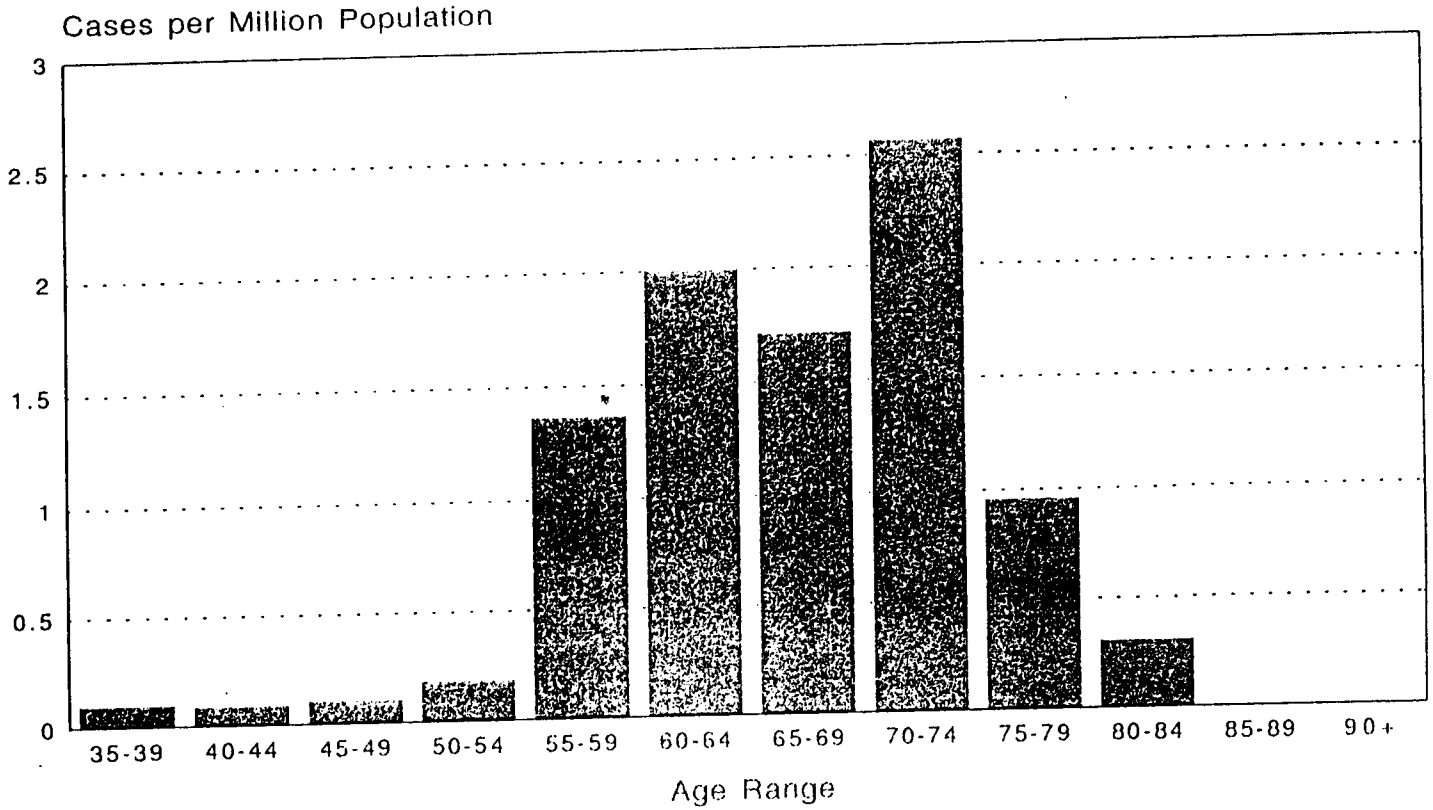


FIGURE 4

CREUTZFELDT-JAKOB DISEASE - SPORADIC CASES

AGE-SPECIFIC INCIDENCE RATES FOR AGE AT DEATH

1990-1993

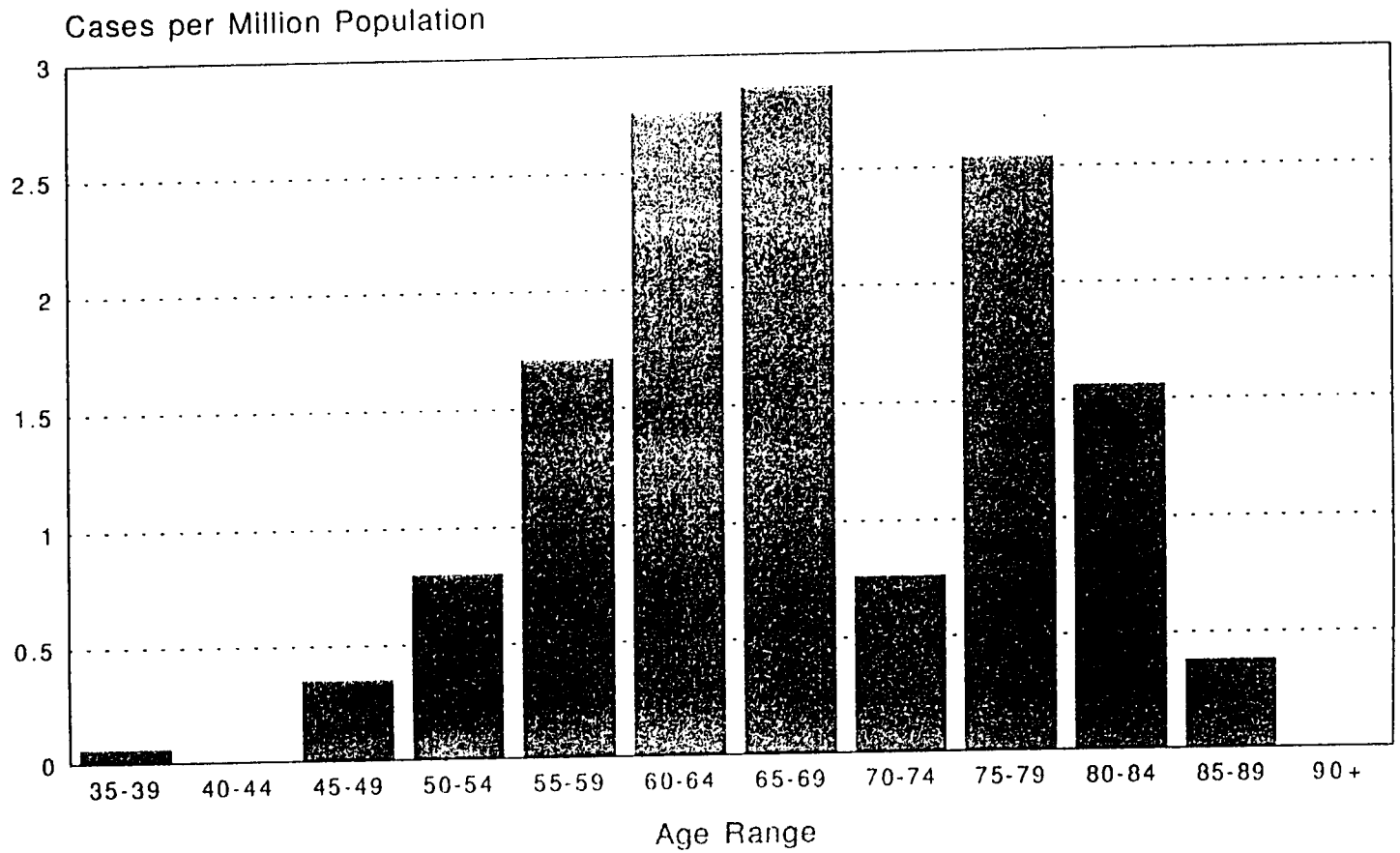


FIGURE 5

SPORADIC CJD
DEATHS FROM 1980-1993
UNDER 75 YEARS OF AGE

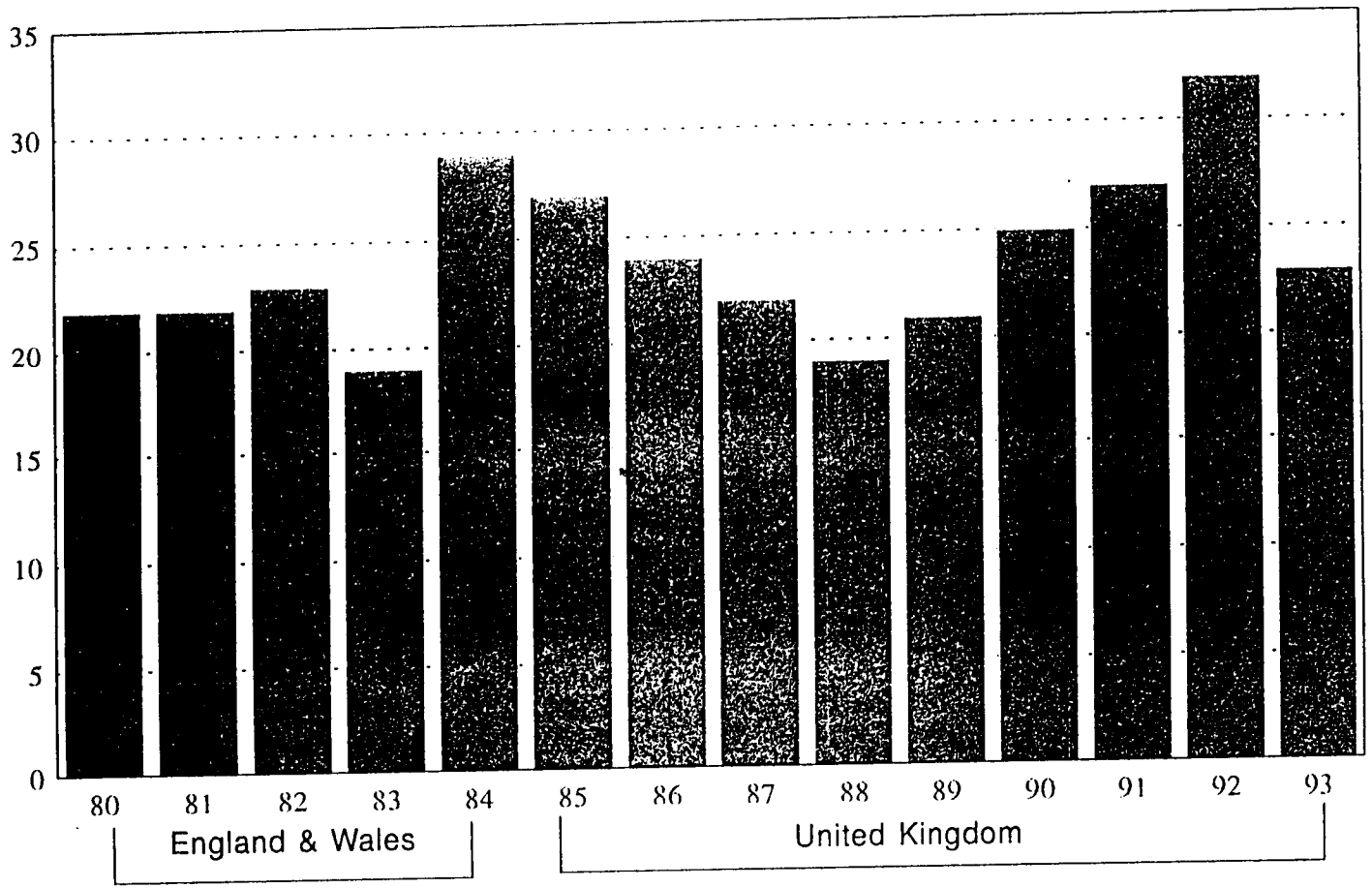


FIGURE 6

SPORADIC CJD
DEATHS FROM 1980-1993
75 YEARS OF AGE AND OVER

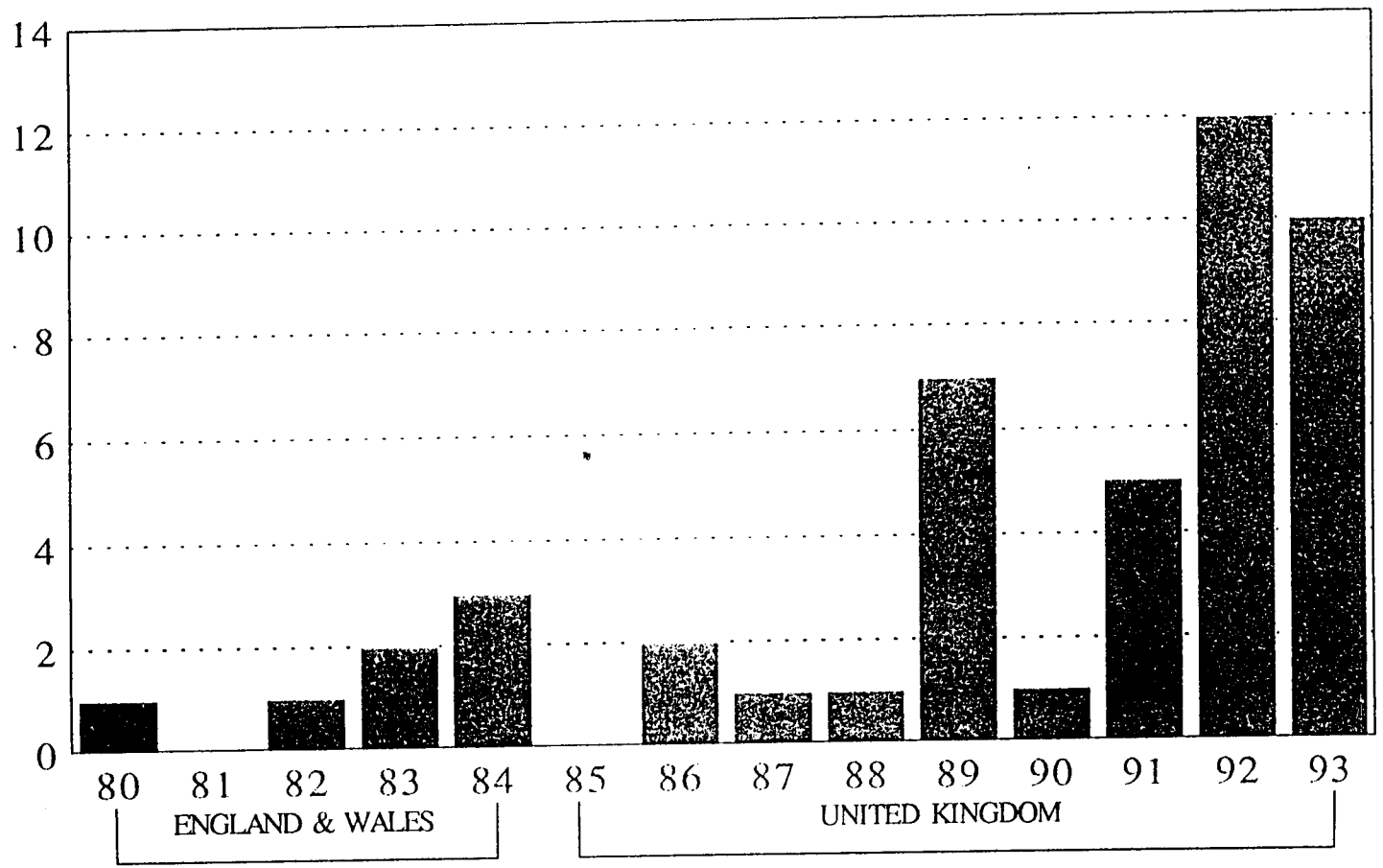


FIGURE 7

SPORADIC CREUTZFELDT-JAKOB DISEASE - DEATHS FROM 1980-1993
75 YEARS OF AGE AND OVER

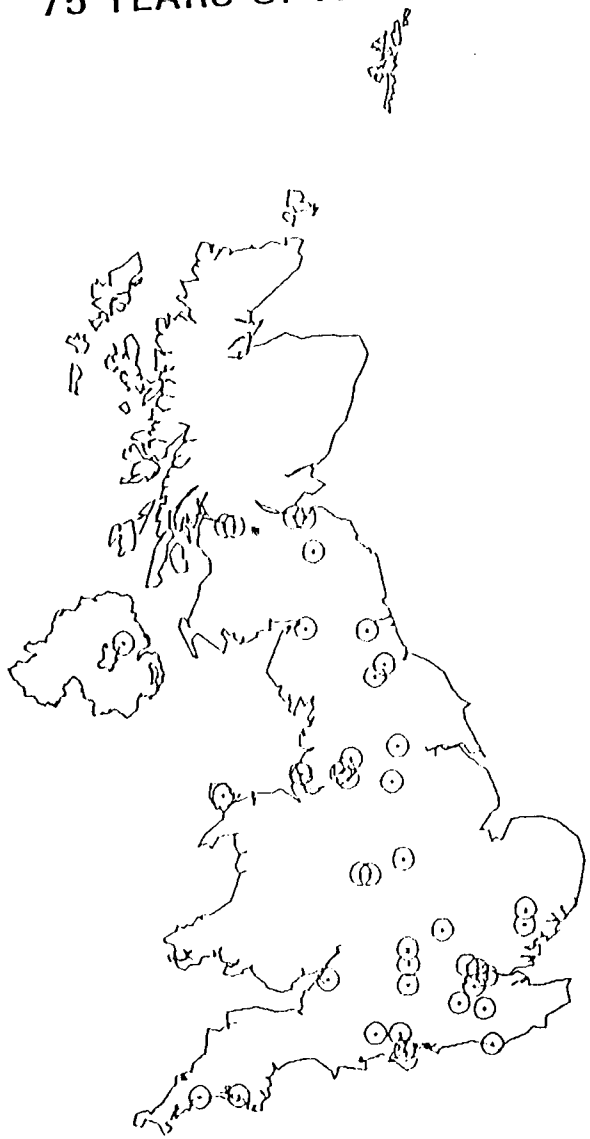


FIGURE 8

CREUTZFELDT-JAKOB DISEASE IN THE UNITED KINGDOM
DEFINITE AND PROBABLE CASES (1 MAY 1990 - 30 APRIL 1994)

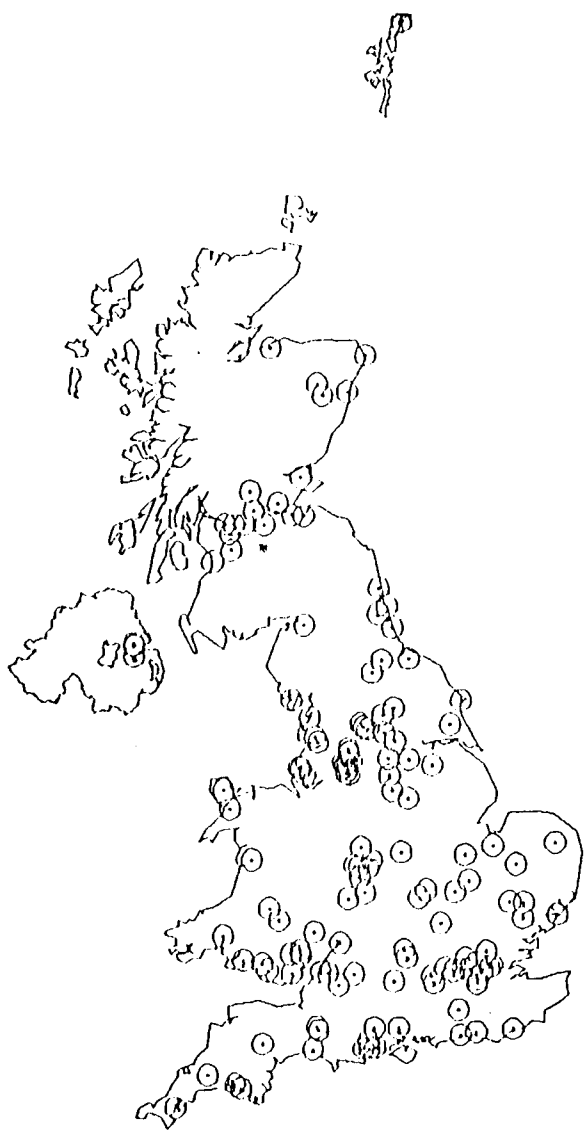


FIGURE 9

SMRs BY STANDARD REGION, 1970-1984

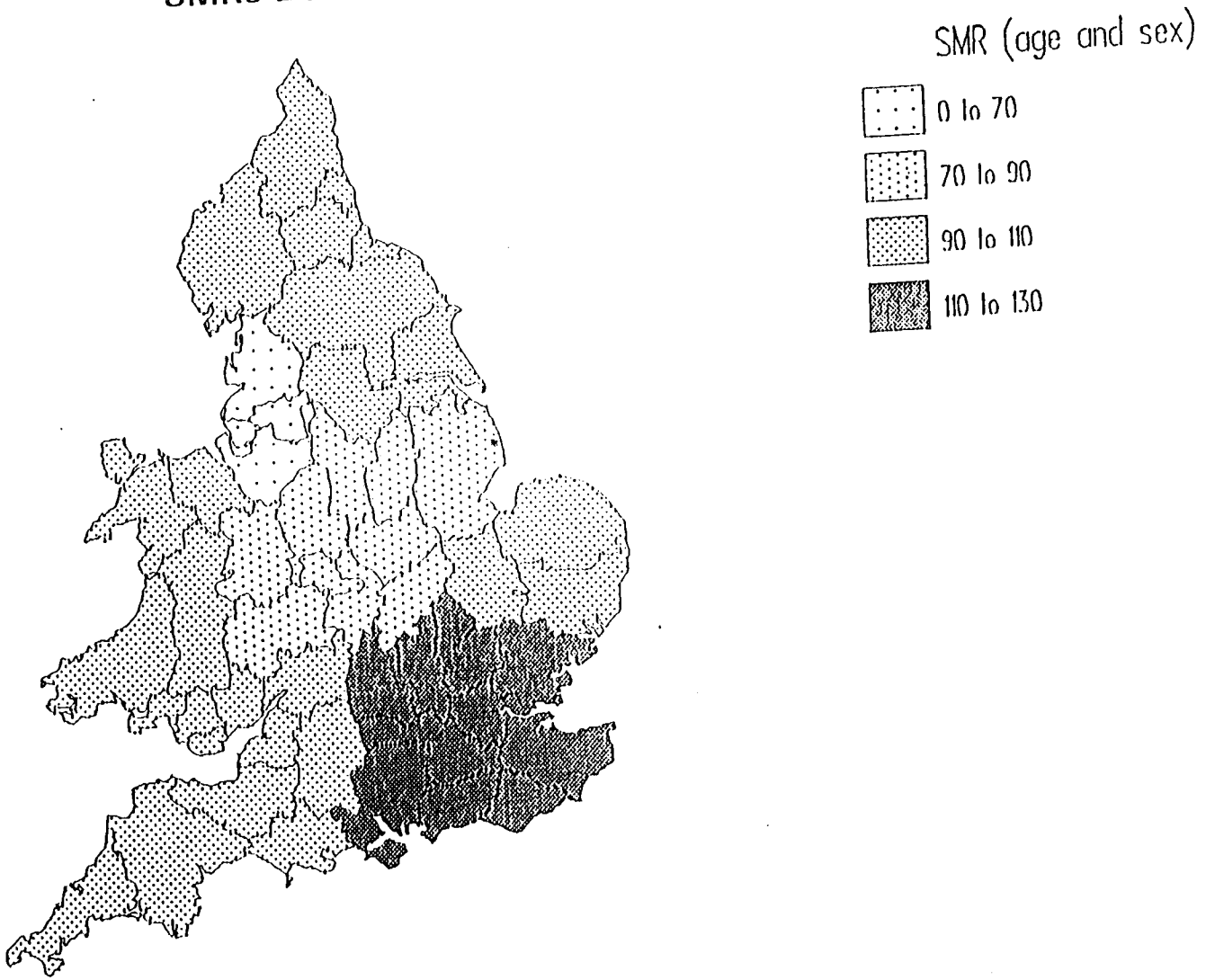


FIGURE 10

SMRs BY STANDARD REGION, 1985-1994

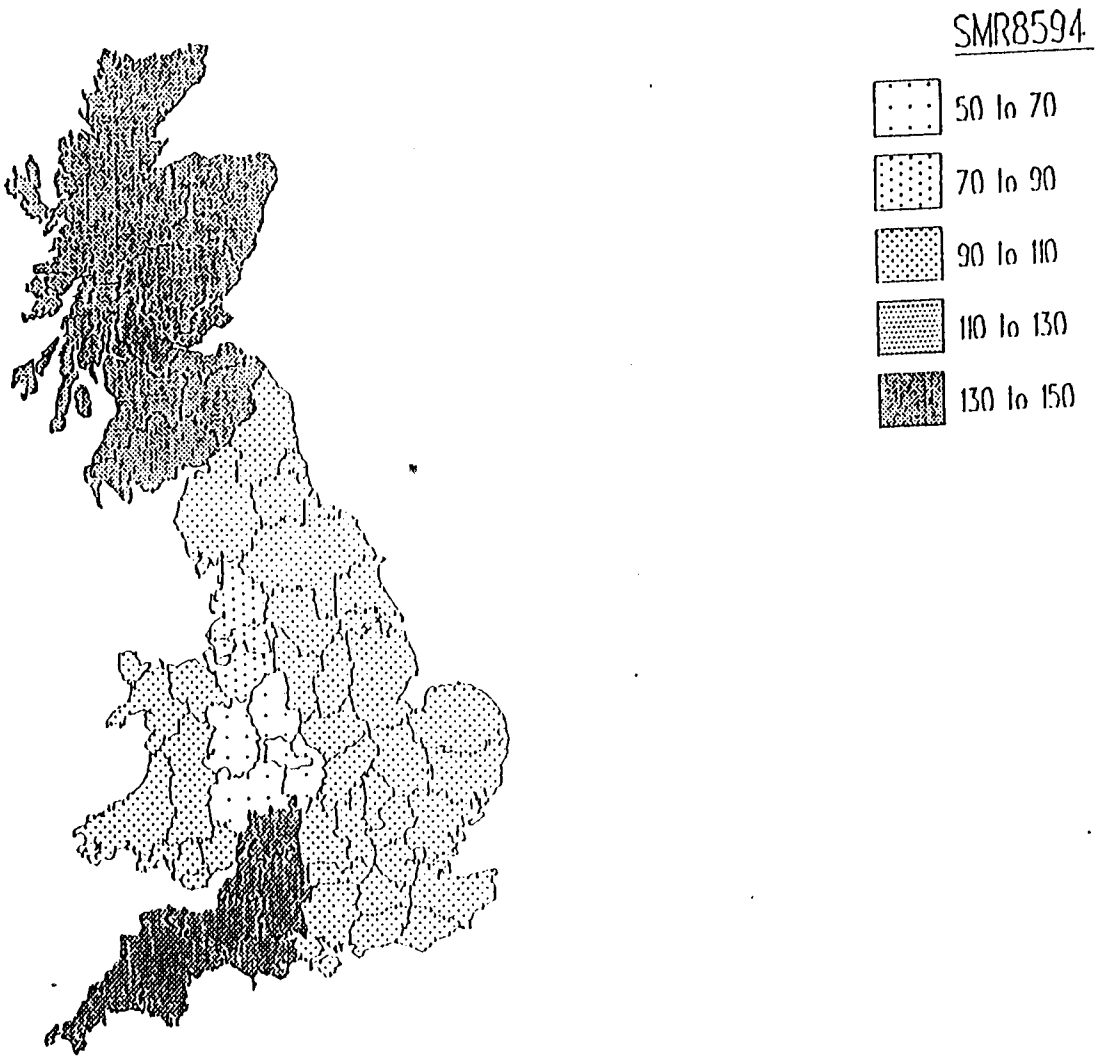


FIGURE 11

MORTALITY BY COUNTY, 1970-1984

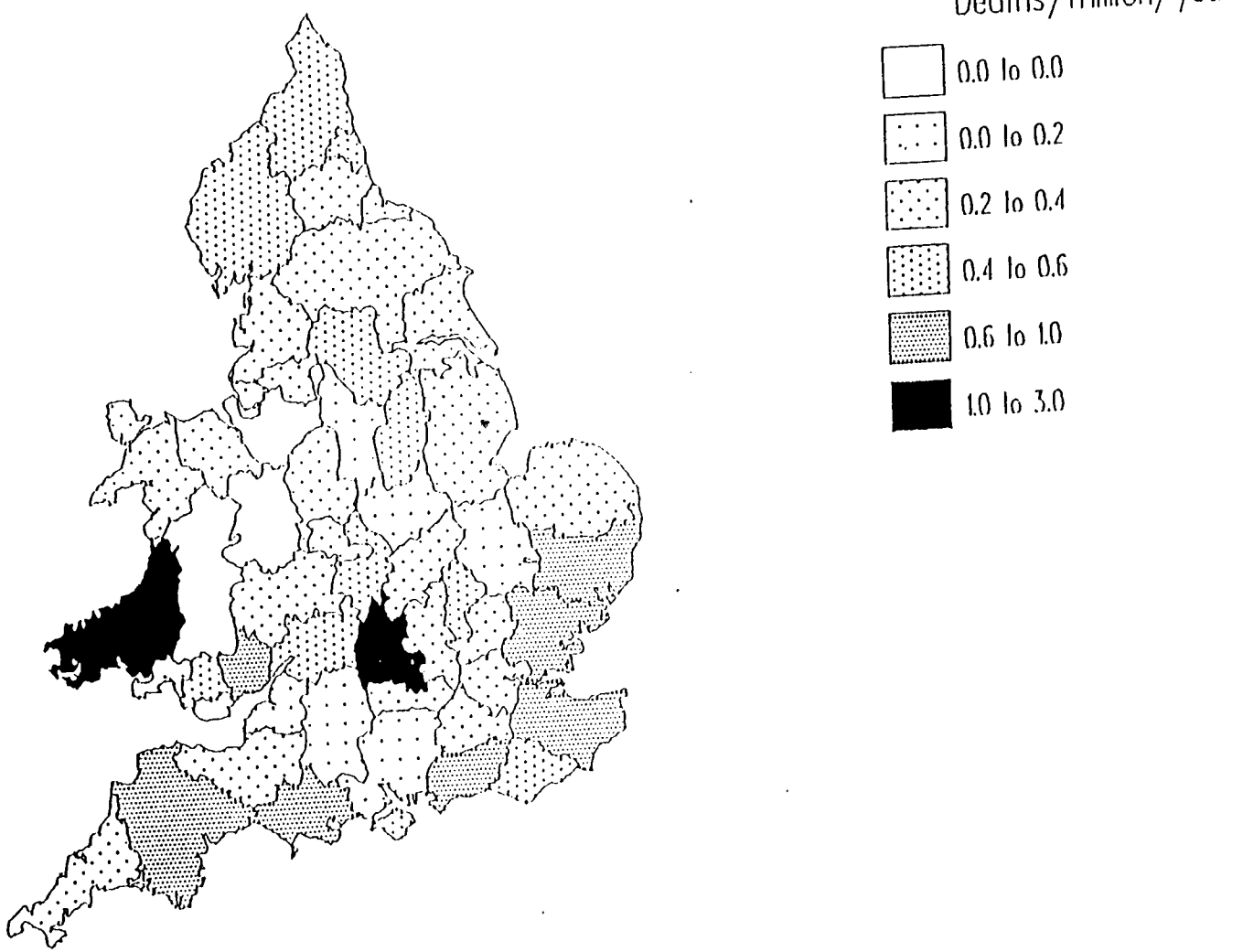


FIGURE 12

MORTALITY BY COUNTY, 1985 - APRIL 1994

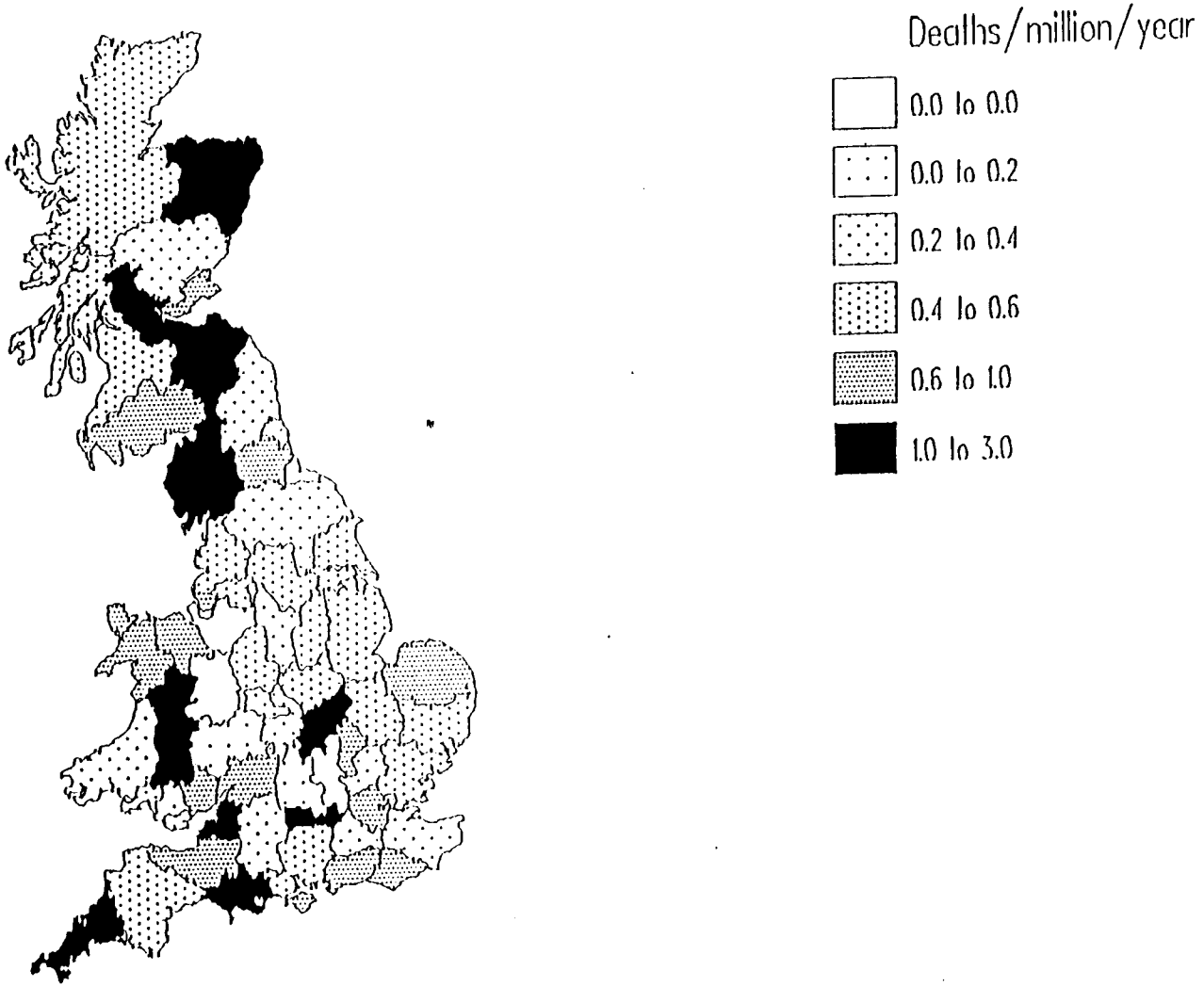


FIGURE 13

CASE-CONTROL STUDY (n = 109)
LOCATION OF VEAL EATERS AMONG CASES (n = 32)

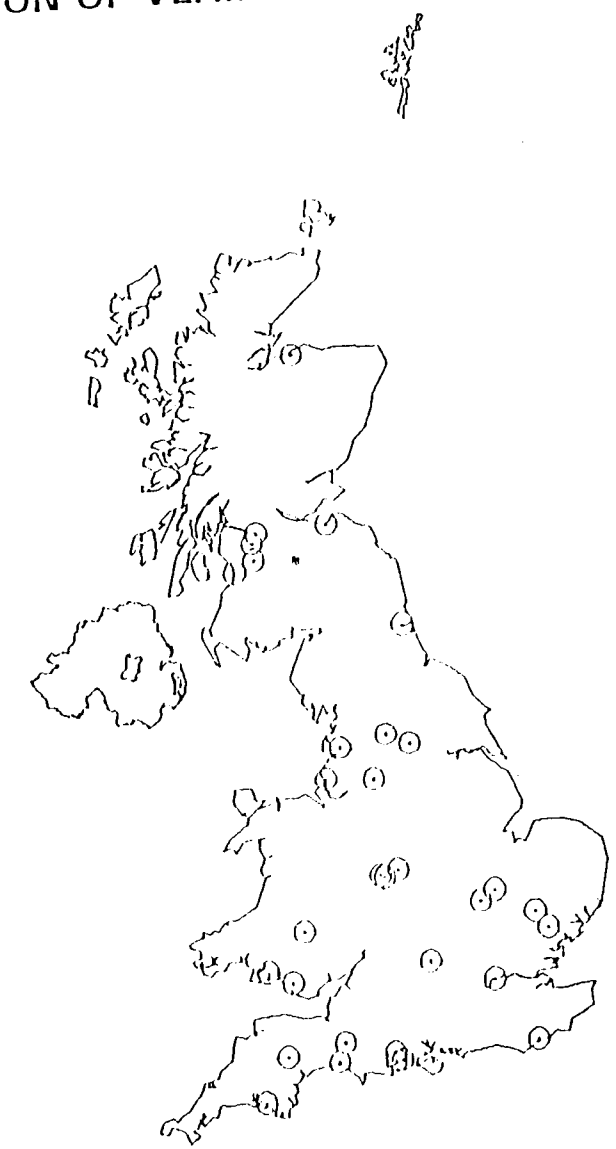
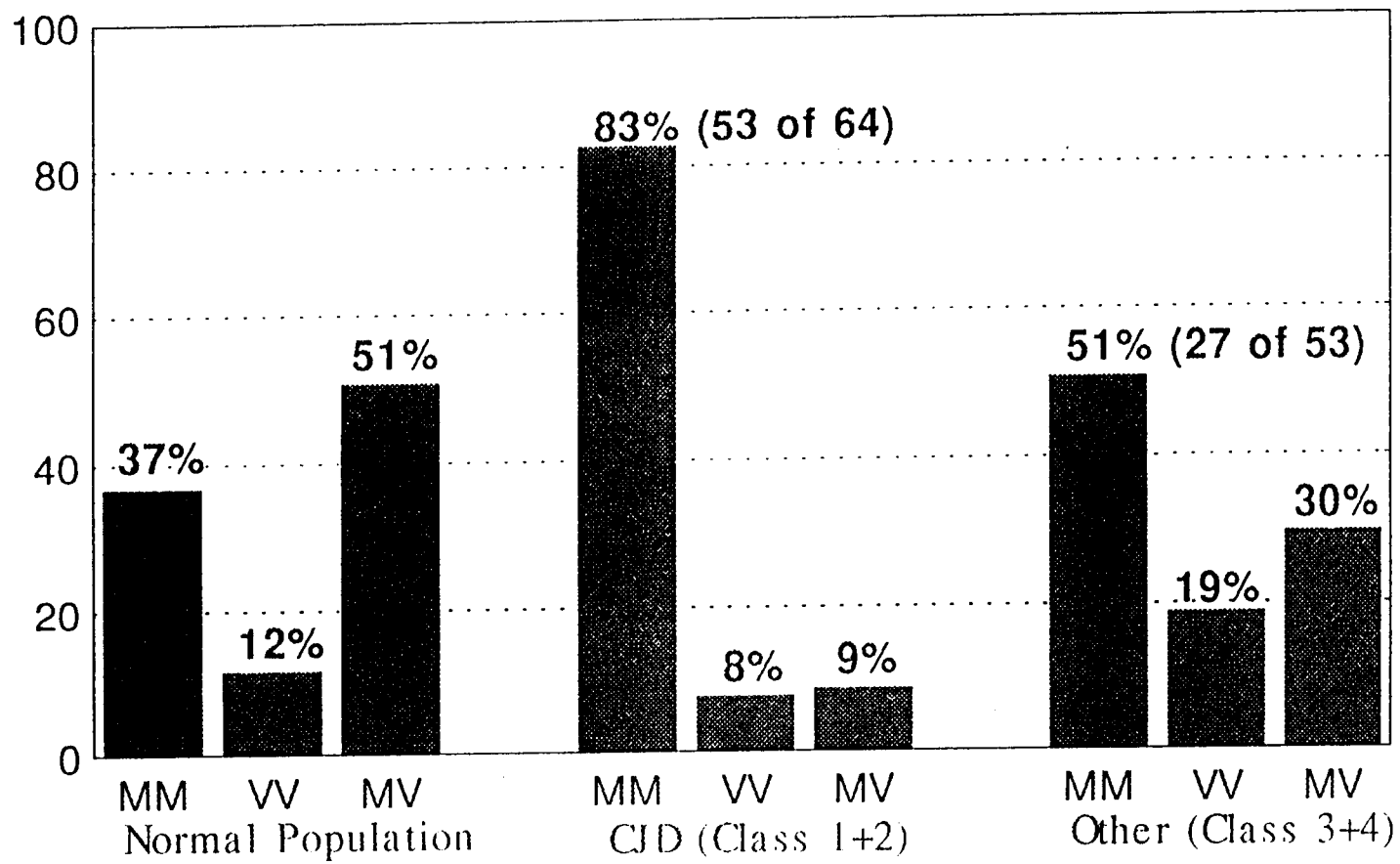


FIGURE 14

DISTRIBUTION OF CODON 129 POLYMORPHISM IN SPORADIC CREUTZFELDT-JAKOB DISEASE COMPARED TO THE NORMAL CAUCASIAN POPULATION



SECTION 2 NEUROPATHOLOGICAL VALIDATION

STATEMENT OF PROGRESS

The third year of the neuropathology surveillance project has continued the work of neuropathological examination, diagnostic validation and research on cases referred to the Unit either for full autopsy or for detailed brain examination following autopsy elsewhere in the country. The formal collaborations with neuropathologists elsewhere in the UK (particularly Dr J. McLaughlin at the Royal Free Hospital and Dr J.M. Mackenzie at the Walton Hospital, Liverpool) has been continued and provides a more secure basis to ensure that autopsies are performed on a high proportion of suspected cases of CJD in the UK. Numerous contacts have been made with pathologists throughout the UK concerning autopsy protocols and techniques, and close links with other neuropathologists in the UK have ensured that diagnostic notification on the basis of pathological findings is provided even in cases where the diagnosis was not made clinically prior to death.

The neuropathologists working on this project (Dr James W Ironside and Dr Jeanne E Bell) are supported by a full time MLSO2 and two part-time secretaries. In addition to the validation project, research projects are undertaken under the auspices of the Medical Research Council and the Agricultural and Food Research Council which support two post doctoral scientists (Dr I. Goodbrand and Dr K. Sutherland) and two further technical staff. These investigative projects are complementary to the diagnostic surveillance project, and new techniques for the automated analysis of prion protein immunocytochemistry have now been established. Extensive research is being undertaken at present in mapping the distribution of the prion protein in the CNS and other tissues in cases of Creutzfeldt-Jakob disease, and studying the pattern of protein deposition in relation to other histological features of the disease, clinical features and PrP genotype. A wide range of antibodies to PrP have been obtained from collaborators in other centres, both within and outside the UK, particularly Dr C. Birkett, Institute for Animal Health, Compton.

The CJD Surveillance Unit laboratory remains a central source for guidance and advice concerning issues of health and safety, particularly since the infectious

agent responsible for spongiform encephalopathies in man have been reclassified into Category 3. Detailed safety protocols are constantly updated, and are widely distributed to colleagues within the UK and in other countries. Dr J.E. Bell is a member of the ACDP Working Party on Spongiform Encephalopathies whose guidelines on working in this field are about to be published (Precautions for Work with Human and Animal Transmissible Spongiform Encephalopathies: ACDP: HMSO).

TISSUE HANDING AND STORAGE

The CJD Surveillance Unit laboratory has been able to establish a tissue and organ bank for cases of Creutzfeldt-Jakob disease, including both fixed and frozen tissues from the CNS and other organs. These are used in collaborative research projects with the Centre for Genome Research in Edinburgh (Professor R. Lathe), the Prion Group in St. Mary's Hospital London (Dr J. Collinge), the University of Nottingham (Professor R. Mayer and Dr J. Lowe) and the University of Manchester (Dr D. Mann). Collaborative research has involved exchange of materials with other centres in the EC and particularly with Dr Paul Brown at NIH, Bethesda, USA.

The increasing complexity of tissues and cases stored in the unit will shortly require the establishment of a computerised database to facilitate accurate record keeping for the tissue bank activities.

COLLABORATION WITH OTHER CENTRES

As in previous years, a close collaboration has been maintained with the AFRC/MRC Neuropathogenesis Unit, University of Edinburgh, particularly with Dr J. Hope and colleagues to whom we are grateful for supplying antibodies to the prion protein. An extensive number of research activities occur with collaboration between the CJD Surveillance Unit and the Neuropathogenesis Unit, particularly on electronmicroscopy and immunocytochemistry. Close collaboration has been maintained with the Centre for Genome Research in the University of Edinburgh (Professor R. Lathe) and this has resulted in several completed studies of pathology, clinical features and genotype in Creutzfeldt-Jakob disease (see reference list).

Continued collaboration with the Prion Disease Group in St. Mary's has been maintained, particularly with regard to the provision of material for genetic analysis. Collaborative projects have also involved colleagues in the University of Nottingham (Dr J. Lowe) and the University of Manchester (Dr D. Mann).

The CJD Surveillance Unit Laboratory maintains a number of collaborative contacts with colleagues overseas, particularly Dr Paul Brown in the NIH, Bethesda, USA and numerous colleagues in EC centres.

Dr Ironside is involved in the BIOMED1 Concerted Action on CJD Surveillance as a reference pathologist, with presentations to meetings in Paris and Rome during 1993/94. Dr Ironside is also involved in the proposed EC Concerted Action on the Neuropathology of Human Spongiform Encephalopathies and has attended two preliminary meetings in Brussels (Chairman Professor H. Budka, Vienna) to present the UK experience of pathological validation and surveillance. This has generated considerable interest in other EC centres, with requests for dissemination of laboratory protocols and diagnostic opinions on referred cases. It is anticipated that the role of the unit as an EC reference centre will increase in the near future.

LABORATORY VISITORS

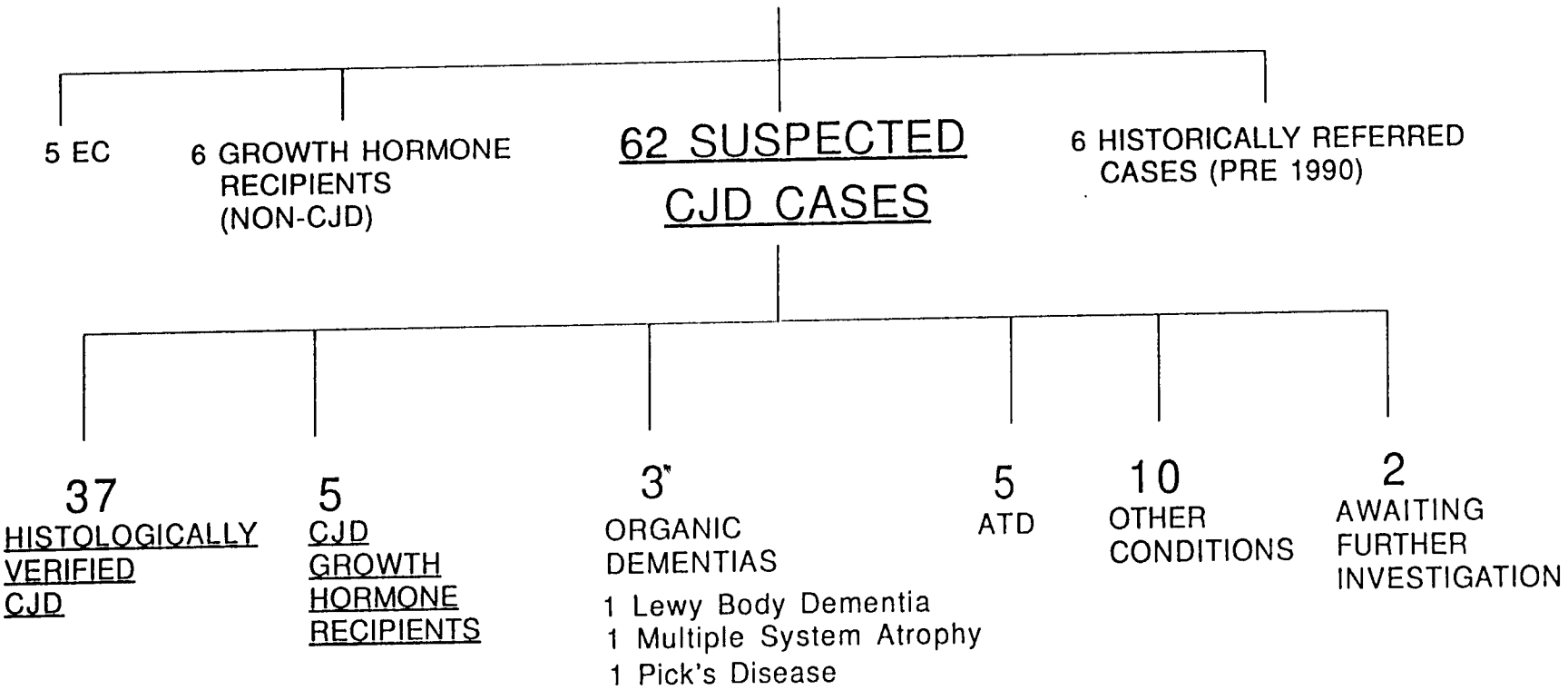
A large number of visitors came to the surveillance unit laboratory during 1993/94 including technical staff, neuropathologists, clinicians, scientists and other workers in the field of human spongiform encephalopathies. Particular interest has been paid to laboratory management and safety protocols, including those for tissue handling and storage.

SURVEILLANCE AND WORKLOAD DURING 1993/94

Please refer to Table 16 on page 50 for surveillance and workload from 1 May 1993 - 30 April 1994.

TABLE 16

NEUROPATHOLOGY OF CREUTZFELDT-JAKOB DISEASE
1 MAY 1993 - 30 APRIL 1994
79 CASES EXAMINED



Comment:
There has been an increase in the number of growth hormone recipient cases investigated, including both those with a diagnosis of Creutzfeldt-Jakob disease and those dying without any apparent neurological abnormalities. These cases are undergoing detailed investigation and a separate report will be prepared later this year.

MEDICOLEGAL ACTIVITIES

Dr J.W. Ironside has been summonsed as an Expert Witness for the Crown at inquests held on the deaths of growth hormone recipients with Creutzfeldt-Jakob disease.

PUBLICATIONS

1. Will RG. Prion Disease. Lancet 1990; 336: pp369.

2. Will RG. Subacute spongiform encephalopathies. In: Current Medicine 3, Ed. D.H. Lawson, Published: Churchill Livingston, Edinburgh. 1991; Chapter 9 pp 127-143.

3. Will RG. Comment: Slow virus infection of the central nervous system. Current Medical Literature (Neurology), 1991 Volume 7, Number 3, September 1991, pp 67-69.

4. Will RG. An overview of Creutzfeldt-Jakob disease associated with the use of human pituitary growth hormone. Develop. Biol. Standard 1991; Vol 75: 85-86.

5. Will RG. Is there a potential risk of transmission of BSE to the human population and how may this be assessed? In: Subacute Spongiform Encephalopathies - Proceedings of a Seminar in the CEC Agricultural Research Programme held in Brussels, 12-14 November 1990. Eds: R. Bradley, M. Savey & B. Marchant. Published by Kluwer Academic Publishers 1991.

6. Will RG. Epidemiological surveillance of Creutzfeldt-Jakob disease in the United Kingdom. Eur. J. Epidemiol. 1991; 7(5): 460-465.

7. Will RG. The spongiform encephalopathies. JNNP 1991; 54(9): 761-763.

8. Esmonde TFG, Will RG. Magnetic resonance imaging in Creutzfeldt-Jakob disease. Ann. Neurol. 1992; 31(2): 230.

9. Brown P, Preece MA, Will RG. 'Friendly fire' in medicine: hormones, homografts and Creutzfeldt-Jakob disease. Lancet 1992; 340: 24-27.

10. EsmondeTFG, Will RG. Transmissible Spongiform Encephalopathies and their Relationship to Human Neurodegenerative Disease. British Journal of Hospital Medicine 1992; 49(6): 400-404.

11. Will RG, Esmonde TFG, Matthews WB. Creutzfeldt-Jakob Disease Epidemiology. In: Prion Diseases of Humans and Animals. Eds: Prusiner SB, Collinge J, Powell J, Anderton B. 1992; ppp 188-199.

12. Esmonde TFG, Will RG. Creutzfeldt-Jakob disease in Scotland and Northern Ireland 1980-1989. Scottish Medical Journal 1992; 37: 181-184.

13. Scott PR, Aldridge BM, Clarke M, Will RG. Bovine spongiform encephalopathy in a cow in the United Kingdom. JAVMA 1989;195; 1745-1747.

14. Will RG. BSE and the spongiform encephalopathies. In: Recent Advances in Clinical Neurology. Ed: Kennard C. 1992; Chapter 5, pp 115-127.

15. Esmonde TFG, Will RG, Slattery JM, Knight R, Harries-Jones R, de Silva R, Matthews WB. Creutzfeldt-Jakob Disease and Blood Transfusion. Lancet 1993;341: 205-207.

16. Esmonde TFG, Lueck CJ, Symon L. Duchen LW, Will RG. Creutzfeldt-Jakob Disease and Lyophilised Dura Mater Grafts: Report of Two Cases and a Review of the Literature. JNNP 1993; 56: 999-1000.

17. Sawcer SJ, Yuill GM, Esmonde TFG, Estibeiro P, Ironside JW, Bell JE, Will RG. Creutzfeldt-Jakob disease in an individual occupationally exposed to BSE. Lancet 1993; 341: 642.

18. Will RG. Prions in animals. Virus and Life 1992; 4: 6--8.

19. Will RG, Ironside JW, Bell JE. Bovine spongiform Encephalopathy and risk to health. BMJ 1992; 305: 53.

20. Department of Health National Surveillance of Creutzfeldt-Jakob Disease. Bell JE and Ironside JW. Bulletin of the Royal College of Pathologists, April 1991, pp 9-10.

21. Bell JE, Ironside JW, McCardle L & Will RG. Creutzfeldt-Jakob disease - UK Neuropathology Project. Neuropathology and Applied Neurobiology 1992; 18: 302.

22. Ironside JW, Bell JE, McCardle L & Will RG. Neuronal and glial reactions in Creutzfeldt-Jakob Disease. Neuropathology and Applied Neurobiology 1992; 18: 295.

23. Ironside JW, McCardle L, Hayward P & Bell JE. Ubiquitin immunocytochemistry in human spongiform encephalopathies. Neuropathology and Applied Neurobiology 1993; 19: 134-140.

24. Prion Protein: Distribution and Significance in Creutzfeldt Jakob disease - Thesis submission by Philip Hayward for Degree of Honours BSc (Medical Science) in Department of Pathology.

25. Bell JE, Ironside JW. How to tackle a possible CJD necropsy. J Clin Path 1993; 46: 193-197.

26. Ironside JW, Bell JE, Hayward P. Glial and neuronal reactions in Creutzfeldt-Jakob disease. Clinical Neuropathology 1992; ii: pp226.

27. Ironside JW, Barrie C, McCardle L & Bell JE. Microglial cell reactions in human spongiform encephalopathies. Neuropathology & Applied Neurobiology 1993; 19(2): 57.

28. Bell JE, Ironside JWI. Neuropathology of spongiform encephalopathies in humans. B. Med. Bull. 1993; 49: 738-777.

29. Prion Protein Pathology in Sporadic Creutzfeldt-Jakob Disease. Thesis submission to Edinburgh University by Simon Thomas MacDonald for the degree of BSc (Hons) (Med Sci) in the Department of Pathology 1994.

30. Tobias E, Mann C, Bone I, de Silva R, Ironside JW. A case of Creutzfeldt-Jakob disease presenting with cortical deafness (Letter). JNNP 1994; 57(7): 872-873.

31. Sutherland K, Ironside JW. A novel application of image analysis to the detection of spongiform change. Analytical and Quantitative Cytology and Histology (In Press).

32. Sutherland K, Barrie C and Ironside JW. Automatic quantification of amyloid plaque formation in human spongiform encephalopathy. Neurodegeneration (In Press).

33. de Silva R, Ironside JW, McCardle L, Esmonde T, Bell J, Will R, Windl O, Dempster M, Esitbeiro P, Lathe R. Neuropathological phenotype and "prion protein" genotype correlation in sporadic Creutzfeldt-Jakob disease. Neuroscience Letters (In Press).

34. Alperovitch A, Brown P, Weber T, Pocchiari M, Hofman A and Will R. Incidence of Creutzfeldt-Jakob disease in Europe in 1993 (Letter). Lancet 1994; 343: 918.

35. de Silva R, Esmonde TFG. Iatrogenic transmission of Creutzfeldt-Jakob disease: an update. CNS Drugs (In Press).

36. Will RG and Wilesmith JW. Response to the article: "Vertical transfer of prion disease" by Lacey and Dealler. Human Reproduction (In Press).

37. Will RG. Epidemiology of Creutzfeldt-Jakob disease. British Medical Bulletin 1993; 49: 960-971.

38. Gray F, Chretien F, Cesaro P, Chatelain J, Beaudry P, Laplanche JL, Mikol J, Bell J, Gambetti Degos. Creutzfeldt-Jakob disease and cerebral amyloid angiopathy. Acta Neuropathol 1994; 88: 106-111.

39. Nicholl D, Windl O, de Silva R, Sawcer S, Dempster M, Ironside JW, Estibeiro JP, Yuill GM, Lathe R, Will RG. Inherited Creutzfeldt-Jakob disease in a British family associated with a novel 144 base pair insertion of the prion protein gene. JNNP (in press).

WORKERS ON CJD PROJECT

CLINICAL

Dr R.G. Will
Dr T.F.G. Esmonde (1990-1992)
Dr R. de Silva (1992-1994)
Dr M. Zeidler (1994 -)
Miss J. Mackenzie

NEUROPATHOLOGY LABORATORY

Dr J.W. Ironside
Dr J.E. Bell
Mrs L. McCardle
Ms A. Honeyman
Ms A. Boyd

RESEARCH STAFF FUNDED BY OTHER SOURCES

Dr K. Sutherland (AFRC)
Dr I. Goodbrand (MRC)
Miss C. Barrie (AFRC)
Mr D. Nicolson (MRC)

MOLECULAR BIOLOGY

Dr J. Collinge, Prion Disease Group, St. Mary's Hospital, London.
Dr O. Windl, Centre for Genome Research, University of Edinburgh.

STATISTICAL ANALYSIS

Professor P. Smith, London School of Hygiene and Tropical Medicine.
Mr S. Cousens, London School of Hygiene and Tropical Medicine.

APPENDICES

method of case ascertainment was through direct notification, mainly from neurologists, and was similar to previous epidemiological surveys of CJD.[2,3] We report results on the comparative incidence of CJD in participating countries for the year 1993:

	France	Germany	Italy	Netherlands	UK
Definite CJD	6	6	11	2	24
Probable CJD	22	13	20	8	8
Total	28	19	31	10	32
Incidence/million person-years	0·50	0·47*	0·54	0·68	0·56

*Extrapolated from figures available from June to December, 1993

The incidence figures are inevitably preliminary because of the likelihood that further cases of CJD will be identified—for example, through the results of post-mortem examinations, which may be delayed. Therefore, the incidence figures relate to cases notified in 1993 and not to mortality rates.

The incidence of CJD in all participating countries is very similar and is also consistent with earlier results.[2,3] This finding contrasts with the striking variation in incidence of BSE: there have been more than 100 000 cases of BSE in the UK, 5 in France, 1 in Germany, and none in Italy or the Netherlands. The disparity between the incidence of CJD and that of BSE suggests that the emergence of BSE has not resulted in a change in the frequency of the occurrence of CJD in 1993.

Although this evidence does not suggest a change in the incidence of CJD that can be attributable to BSE, it will be many years before any such change can be excluded because of the potentially long incubation periods in the spongiform encephalopathies. The continuing systematic study of the epidemiological indices of CJD in several countries with or without BSE will provide important comparative information on the relative risk of CJD in relation to animal spongiform encephalopathies.

A Alperovitch, P Brown, T Weber, M Pocchiari, A Hofman, R Will

INSERM U360, Villejuif, France; Laboratory of CNS Studies, National Institutes for Health, Bethesda, USA; Neurologische Klinik und Poliklinik der Georg-August-Universität Göttingen, Göttingen, Germany; Registro Nazionale della Malattia di Creutzfeldt-Jakob, Istituto Superiore di Sanità, Roma, Italy; Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, Netherlands; and National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh EH4 2XU, UK

1 Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM. Creutzfeldt-Jakob Disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol* 1979; 5: 177–88.

2 Will RG, Matthews WB, Smigh PG, Hudson C. A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970–1979 II: epidemiology. *JNNP* 1986; 49: 749–55.

3 Brown P, Cathala F, Raubertas RF, Gajdusek DC, Castaigne P. The epidemiology of Creutzfeldt-Jakob disease: conclusion of a 15-year investigation in France and review of the world literature. *Neurology* 1987; 37: 895–904.

Incidence of Creutzfeldt-Jakob disease in Europe in 1993

SIR—Epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted in the UK in 1990 to evaluate any changes in the pattern of the disease that might be attributable to bovine spongiform encephalopathy (BSE). In 1993 a project for coordination of national CJD surveillance programmes was funded by the EC, linking already established or proposed national registers in France, Germany, Italy, Netherlands, and UK. Cases are classified as definite or probable according to diagnostic criteria adapted from Masters et al,[1] which are common to all participating countries. The

1994, 15, 105-112

No. 15

World Health Organization, Geneva

Organisation mondiale de la Santé, Genève

WEEKLY EPIDEMIOLOGICAL RECORD

RELEVÉ ÉPIDÉMIOLOGIQUE HEBDOMADAIRE

15 APRIL 1994 • 69th YEAR

69e ANNÉE • 15 AVRIL 1994

CONTENTS — SOMMAIRE

Veterinary public health and Mental health – Possible Creutzfeldt-Jakob disease in an adolescent, United Kingdom	105	Santé publique vétérinaire et Santé mentale – Cas suspect de maladie de Creutzfeldt-Jakob chez une adolescente, Royaume-Uni	105
Cancer – Mortality trends for selected smoking-related cancers and breast cancer, 1950-1990, United States of America	107	Cancer – Tendances de la mortalité pour certains cancers liés au tabagisme et pour le cancer du sein, 1950-1990, Etats-Unis d'Amérique	107
List of infected areas	110	Liste des zones infectées	110
Influenza	112	Grippe	112
Diseases subject to the Regulations	112	Maladies soumises au Règlement	112

Veterinary public health and Mental health

Possible Creutzfeldt-Jakob disease in an adolescent

United Kingdom. The occurrence of a suspect case of Creutzfeldt-Jakob disease (CJD) in an adolescent in the United Kingdom has fuelled speculation about a possible link between bovine spongiform encephalopathy (BSE) and CJD.

Case report

A 15-year old girl was admitted to hospital in 1993 for investigation of secondary amenorrhoea for 5 months, followed by lethargy, poor concentration, tearfulness, involuntary movements and weight loss. She had persistent dry cough. On admission there was evidence of generalized chorea but no other focal neurological signs. Over the next 4 weeks there was progressive deterioration with the development of memory impairment, cerebellar ataxia and myoclonus, culminating in a state of akinetic mutism.

Detailed and extensive investigation revealed no significant abnormality, excluding a range of possible diagnoses including subacute sclerosing panencephalitis and Wilson's disease. Serial EEGs were diffusely abnormal but did not show specific diagnostic features.

In view of the diagnostic uncertainty, a brain biopsy was carried out; this showed microvacuolation of the cortical neuropil and some neuronal loss but no cortical gliosis. In addition, there were numerous dilated perivascular spaces in the white matter, some containing fresh haemorrhage. The appearances were thought to be inconclusive, with CJD as one possibility. Subsequent immunostaining for prion protein (PrP) was negative, a finding that provides no support for the diagnosis, although this possibility cannot be excluded.

Subsequently the patient's condition has been static and she remains in an akinetic mute state. Serial EEGs have been carried out and, although showing marked generalized abnormalities, have not as yet shown periodic discharges.

Santé publique vétérinaire et Santé mentale

Cas suspect de maladie de Creutzfeldt-Jakob chez une adolescente

Royaume-Uni. L'observation d'un cas suspect de maladie de Creutzfeldt-Jakob (MCJ) chez une adolescente au Royaume-Uni a relancé la spéculation sur l'éventualité d'un lien entre l'encéphalopathie spongiforme bovine (ESB) et cette maladie.

Observation

Une adolescente de 15 ans, présentant une aménorrhée secondaire depuis 5 mois, avec léthargie, difficultés de concentration, crises de larmes, mouvements involontaires, perte de poids et toux sèche persistante, a été hospitalisée en 1993 pour examen. Au moment de l'admission, on a constaté une chorée généralisée, mais aucun autre signe neurologique en foyer. Au cours des 4 semaines suivantes, son état s'est progressivement détérioré avec altération de la mémoire, ataxie cérébelleuse et myoclonie, pour aboutir à un état de mutisme akinétique.

Des examens approfondis n'ont révélé aucune anomalie significative et ont permis d'éliminer un certain nombre d'hypothèses, notamment une panencéphalite sclérosante subaiguë et la maladie de Wilson. Une série d'électro-encéphalogrammes (EEG) a montré des anomalies diffuses, mais aucune caractéristique spécifique permettant de poser un diagnostic n'a été découverte.

Pour tenter de lever ces incertitudes, une biopsie cérébrale a été pratiquée; celle-ci a révélé une microvacuolisation du neuropile cortical et une déperdition neuronale, mais pas de gliose corticale. En outre, la substance blanche contenait de nombreux espaces périvasculaires dilatés dont certains présentaient des signes récents d'hémorragie. Ces résultats ont été jugés peu concluants et la MCJ a été considérée comme une possibilité. Un test ultérieur de recherche du prion (PrP, de l'anglais *prion protein*) par immunocoloration a donné un résultat négatif qui ne confirme pas ce diagnostic, sans toutefois l'exclure.

Depuis, l'état de la patiente n'a pas évolué et elle reste atteinte de mutisme akinétique. Les EEG présentent des anomalies généralisées marquées, mais on n'a pas encore observé de décharges périodiques.

There is a past history of one febrile convulsion with rubella at the age of 5 and one unexplained collapse at the age of 9. There is no history of any operative procedure and the patient has not been treated with human pituitary derived hormones. There is no family history of dementia and DNA analysis has excluded any known mutation of the PrP gene which has been shown to be associated with prion disease. The patient is a heterozygote at codon 129 of the PrP gene.

Discussion

The diagnosis in this patient remains uncertain, despite cortical biopsy and an extensive range of other investigations. CJD is clearly one diagnostic possibility and this diagnosis may become more likely if the "typical" EEG appearance of CJD develops. A firm diagnosis, however, can only be made following neuropathological examination at post mortem.

The occurrence of sporadic CJD in a patient of this age would be highly unusual, although not without precedent. There have been 3 previous reports of sporadic CJD in teenagers and a further report in a patient aged 20. In none of these cases was there a history of potential iatrogenic exposure, nor a family history of dementia, indicating that these were truly sporadic cases. The possibility of an inherited prion disease has been excluded in the current case by analysis of the PrP gene, although it is of interest that there was a heterozygous genotype at codon 129 of the PrP gene, a genotype that is uncommon in sporadic CJD. No genotype information is available from the previous cases with an early age of onset.

Detailed investigation failed in any of these cases to reveal any obvious environmental source of infection. In the current case a link with any animal spongiform encephalopathy has not been confirmed, although investigation is still in progress. The possibility of the disease developing due to a spontaneous mutational event was raised in one of these case reports, and subsequent scientific evidence has provided support for this theory which does, however, remain unproven and perhaps unprovable.

It is clear that CJD has occurred in young patients in the United States of America, which is free of BSE and in France, which was free of BSE at the time of the patient's clinical illness. In 4 of the 5 cases there cannot therefore be any causative link with BSE. Speculation that the occurrence of CJD in an adolescent in the United Kingdom (should this be proven) is related to BSE should be regarded as tenuous at best in the light of current information.

There is a need for increasing awareness of the potential for CJD to occur in younger age groups, as had already been concluded in a report dated 1981.

(Based on: A report from the National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh, Scotland.)

• A list of references is available on request from the Veterinary Public Health Unit, World Health Organization, 1211 Geneva 27, Switzerland.

Editorial Note: CJD is usually a neurodegenerative disease of late middle life progressing rapidly (duration, up to 2 years). The disease belongs to the group of human transmissible spongiform encephalopathies along with Kuru and Gerstmann-Sträussler syndrome. The clinical picture of CJD consists of a rapidly progressive dementia with movement disorders (especially myoclonus) and a characteristic electroencephalogram. CJD occurs sporadically at a uniform worldwide incidence of 0.5 to 1 case per million population per annum. Some 5-10% of the cases are familial with an apparently dominant pattern of inheritance. A small number of cases have occurred iatrogenically through accidental use of contaminated tissues (e.g., transplants) and neurosurgical instruments.

Parmi les antécédents, on note des convulsions fébriles avec rubéole à l'âge de 5 ans et un collapsus inexpliqué à 9 ans. La patiente n'a jamais subi d'intervention chirurgicale et n'a pas été traitée avec des hormones hypophysaires d'origine humaine. Il n'existe aucun antécédent familial de démence et l'analyse de l'ADN a exclu toute mutation connue du gène PrP, dont le lien avec la maladie à prions a été montré. La patiente est hétérozygote pour le codon 129 du gène PrP.

Analyse

Malgré une biopsie corticale et une longue série d'examens, le diagnostic reste incertain. La MJC fait évidemment partie des possibilités et cette hypothèse se trouverait renforcée si l'EEG présentait les caractéristiques de la maladie. Le diagnostic ne pourrait toutefois être confirmé qu'à la suite d'un examen neuropathologique à l'autopsie.

Un cas sporadique de MJC chez un sujet de cet âge, quoique tout à fait inhabituel, ne serait pas sans précédent. En effet, la maladie a déjà été observée chez 3 adolescents et chez un sujet âgé de 20 ans. Chaque fois, on a pu écarter l'origine iatrogène et constater l'absence d'antécédents familiaux de démence, ce qui signifie qu'il s'agissait bien de cas sporadiques. Dans le cas présent, la possibilité d'une maladie des prions héréditaire a été exclue par l'analyse du gène PrP. Toutefois, il est intéressant de noter le génotype hétérozygote pour le codon 129 du gène PrP, car ce génotype est inhabituel dans les cas sporadiques de MCJ. Aucune information relative au génotype n'est disponible pour les autres jeunes malades.

Pour aucun d'entre eux, et malgré une enquête approfondie, il n'a été possible de mettre en évidence une source d'infection dans l'environnement. Dans le cas actuel, aucun lien n'a pu être confirmé avec une forme quelconque d'encéphalopathie spongiforme animale, mais l'enquête se poursuit. La possibilité qu'une mutation spontanée soit à l'origine de la maladie a été évoquée dans le compte rendu de l'un des cas mentionnés ci-dessus. Des observations ultérieures sont venues étayer cette théorie qui n'a cependant pas été confirmée et qui est peut-être impossible à prouver.

Il est certain que des cas précoces de MJC ont déjà été observés aux Etats-Unis d'Amérique où l'ESB est inconnue, et en France où elle n'existait pas lorsque cette patiente est tombée malade. Dans 4 cas sur 5, l'ESB est donc hors de cause. L'hypothèse selon laquelle la survenue de la MJC chez une adolescente au Royaume-Uni (à supposer que le diagnostic soit confirmé) serait liée à l'ESB est donc pour le moins fragile dans l'état actuel des connaissances.

Il faut cependant être plus conscient du fait que cette maladie peut aussi toucher des sujets jeunes, comme l'avait déjà signalé dans sa conclusion un rapport datant de 1981.

(D'après: un rapport de la *National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital*, Edimbourg, Ecosse.)

• Une liste de références bibliographiques est disponible sur demande auprès de l'unité de Santé publique vétérinaire, Organisation mondiale de la Santé, 1211 Genève 27, Suisse.

Note de la Rédaction: La MCJ est une maladie neurodégénérative apparaissant généralement tard dans le milieu de la vie et évoluant rapidement (durée jusqu'à 2 ans). Elle appartient au groupe des encéphalopathies spongiformes transmissibles humaines avec le Kuru et le syndrome de Gerstmann-Sträussler. Sur le plan clinique, la MCJ est caractérisée par une démence d'évolution rapide accompagnée de mouvements anormaux (myoclonies) et d'un EEG caractéristique. La MCJ apparaît sous forme sporadique avec une incidence annuelle uniforme de 0,5 à 1 cas par million d'habitants dans le monde entier. Quelque 5-10% des cas ont une origine familiale avec une transmission sur un mode héréditaire apparemment dominant. Un petit nombre de cas iatrogéniques ont fait suite à l'utilisation de tissus (greffes, par exemple) ou d'instruments de neurochirurgie contaminés.