A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970–1979 II: epidemiology

RG WILL,* WB MATTHEWS,* PG SMITH,† C HUDSON

From the University Department of Clinical Neurology, Radcliffe Infirmary, Oxford* and the Department of Epidemiology, London School of Hygiene and Tropical Medicine,† UK

SUMMARY A comprehensive search yielded 121 confirmed cases of Creutzfeldt-Jakob disease who died in England and Wales in the decade 1970–1979, 31 probable cases and 10 possible cases. Descriptive epidemiological data are presented. The average annual incidence was 0·3 cases/million. An unexpected female excess was found. There was no evidence of space-time clustering of cases and no associations with occupation or past medical treatment were apparent. There was statistically significant variation in incidence rates in different parts of the country but no relationship was discovered between incidence and population density.

Creutzfeldt-Jakob disease was first transmitted to the chimpanzee in 1968,[1] but despite extensive subsequent investigation no means of natural transmission has been discovered. Lateral transmission of an agent is thought to occur in scrapie,[2] transmissible mink encephalopathy,[3] and kuru[4] but, with the exception of rare cases of iatrogenic transmission and possible contact transmission with familial cases, has not been described in Creutzfeldt-Jakob disease. As part of an epidemiological survey of the disease in England and Wales a retrospective survey was undertaken for the decade 1970–1979. The present communication is concerned with the epidemiological aspects of the survey.

Methods

Cases were ascertained from three sources. The primary source of cases was from death certificates. The 8th ICD revision, which was in use between 1970–1978, did not have a separate code for Creutzfeldt-Jakob disease and it was first necessary to define rubrics likely to include patients dying of Creutzfeldt-Jakob disease. Death certificates for the year 1973 was available on microfilm at the Office of Population Censuses and Surveys, and all certificates coded under rubrics 348, 290·0, 290·1, 333·9, 347·9, 331·9 and 342 were examined for mention of Creutzfeldt-Jakob disease or Subacute Spongiform Encephalopathy. (A list of rubrics is appended.) Two cases certified as Creutzfeldt-Jakob disease were coded under rubric 290·1 and twelve cases under rubric

Address for reprint requests: RG Will, Maida Vale Hospital for Nervous Diseases, 4 Maida Vale, London W9 1TL, UK

Received 13 August 1985
Accepted 10 September 1985

333·9, but there were no cases coded under the other five rubrics.

Details of pathologically confirmed cases were available from a previous study,[5] in which cases were ascertained by direct notification from neurological centres, and death certificates were obtained for 55 of these patients who had died between 1970–1979. Creutzfeldt-Jakob disease was not given as the cause of death nor mentioned on the certificate in 12 cases and of the 43 correctly certified cases 33 were coded under rubrics 333·9 and 781·7. The ten remaining cases were coded under six separate rubrics, the majority of which referred to the terminal cause of death. It was concluded that a high proportion of cases dying of Creutzfeldt-Jakob disease in the nineteen-seventies could be ascertained by examining death certificates coded under rubrics 333·9 and 781·7, and all certificates coded under these rubrics were obtained for the years 1970–1978. In 1979 the 9th ICD revision came into effect with a separate rubric for Creutzfeldt-Jacob disease and these certificates were also obtained.

All neurologists and neuropathologists were asked to notify cases and further cases were ascertained by enquiry at neurological centres. A number of cases not identified from these sources were identified from a list of confirmed cases from the previous study.[5]

Hospital notes were sought for all cases notified as dying of Creutzfeldt-Jakob disease and cases were classified by previously published criteria[6] as definite, probable or possible. In short, a definite diagnosis required rapidly progressive dementia, typical EEG changes, certain commonly encountered clinical signs, and histological confirmation of neuronal loss, astrocytosis and spongiform degeneration of appropriate distribution. "Probable" cases were similar but without histology. In "possible" cases the typical EEG was not required.

Clinical details were obtained in all patients ascertained directly from neurological centres and in those identified from the list of cases held from the previous study. In 20 of the 175 cases ascertained from death certificates no details

could be obtained, although after enquiry at local hospitals it seemed unlikely that Creutzfeldt-Jakob disease was the correct diagnosis in these patients.

Demography
England and Wales are divided into nine standard regions and 53 counties, and statistical data for these administrative areas were obtained from the 1981 census.

Results

Patient numbers A comprehensive search yielded 121 definite cases of Creutzfeldt-Jakob disease dying in the decade 1970–1979, 31 probable cases and 10 possible cases. The total number of cases classified by source and diagnostic category is shown in Table 1. The cases were further subdivided into three clinical types as described in a previous publication on the clinical features of these patients.[7] In brief, subacute cases developed progressive dementia rapidly leading to a vegetative state. The median duration of illness

Table 2 *Deaths classified by clinical type of disease*

Clinical type	Definite/probable cases	Possible cases
Subacute	137	4
Amyotrophic	3	6
Intermediate	12	0
Total	152	10

from first symptoms to death was 4·0 months, with a range from 2 weeks to 18 months. Intermediate cases developed a static or slowly progressive focal neurological deficit for months or years prior to the acute illness (onset to death: median = 29 months, range: 1 month to 5 years). Amyotrophic cases typically developed slowly progressive dementia for a period of years prior to the development of wasting and fasciculation of limb or bulbar musculature (onset to death: median = 27 months, range: 10 months to 9 years). Classification by clinical type is shown in Table 2. The diagnosis of Creutzfeldt-Jakob disease in possible

Table 1   *Deaths from Creutzfeldt-Jakob disease in England and Wales 1970–1979*

Source of cases	Certificates	Certificates/List	List only	Other	Total
Confirmed	39	40	23	19	121
Probable	26	0	0	5	31
Possible	7	1	0	2	10
Totals	72	41	23	26	162

Cases were ascertained from death certificates, from a list of cases already held from a previous study, and by direct enquiry at neurological centres
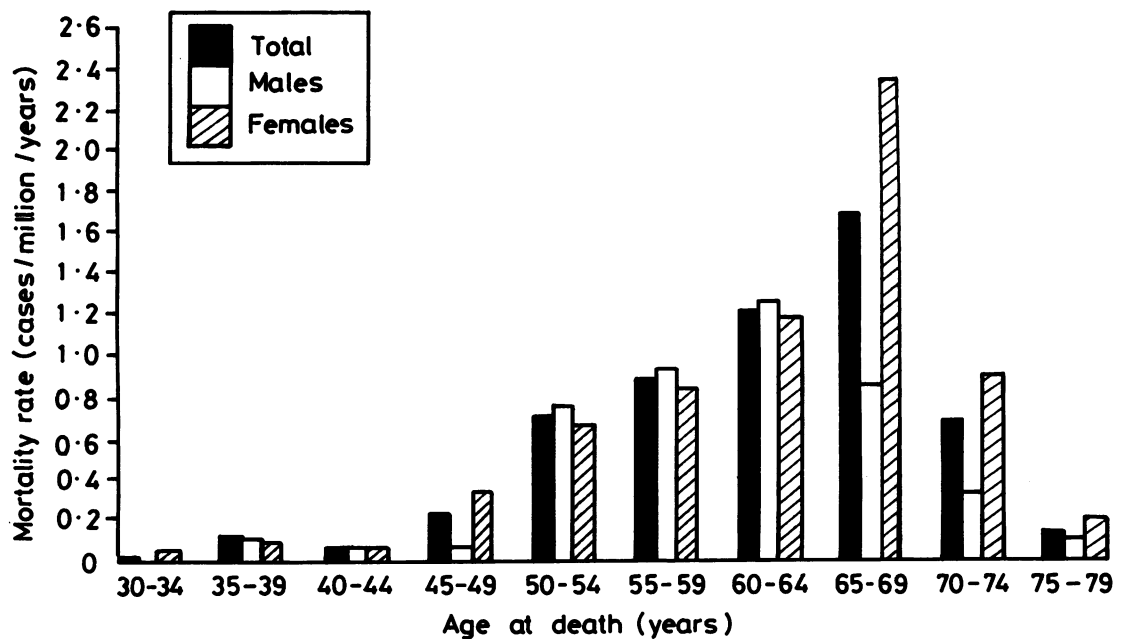

Fig 1   *Age and sex-specific mortality rates for Creutzfeldt-Jakob disease in England and Wales 1970–79 by 5 year age groups. Males are represented by open bars, females by hatched bars and the total mortalities for each age band by solid bars.*

Table 3 . *Number of deaths from Creutzfeldt-Jakob disease by sex and year*

Year of death	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total
Male	3	4	3	8	9	2	4	8	12	6	59
Female	8	9	6	8	9	7	12	12	16	12	99
Total	11	13	9	16	18	9	16	20	28	18	158

Fig 2   *Geographical distribution of cases of Creutzfeldt-Jakob disease in England and Wales 1970–79.*

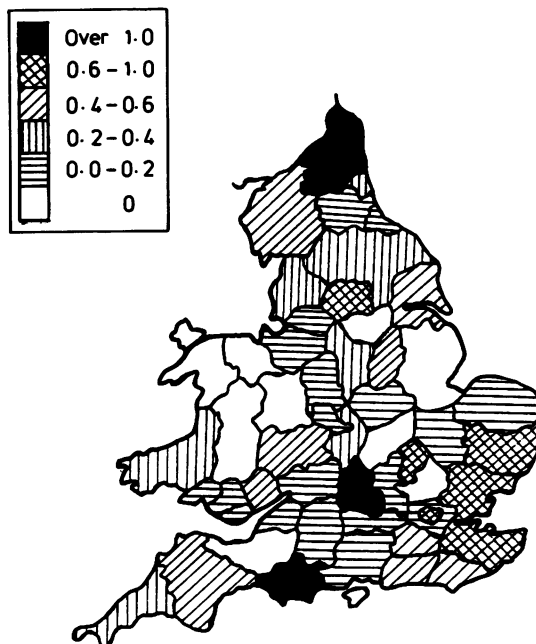|	
■	Over 1·0
▨	0·6 – 1·0
▧	0·4 – 0·6
▥	0·2 – 0·4
▤	0·0 – 0·2
	0

Fig 3   *Mortality rates of Creutzfeldt-Jakob disease by county in England and Wales 1970–79. Solid areas represent centres of highest incidence and blank areas those of lowest incidence.*

subacute cases cannot be made with confidence and these cases were excluded from all subsequent analyses, which therefore include 158 cases.

Age and sex distribution   Of the total of 158 cases, 99 were female and 59 male, a ratio of 1·68:1. Figure 1 shows age specific mortality rates in 5 year age groups. The peak mortality was in the 65–69 year age group with the great majority of patients dying between the ages of 50 and 69 years. There was a marked decrease in incidence over the age of 69. No cases aged 80 years or over were discovered. The excess of female cases was predominantly among those dying at age 65 years or more, at which ages the female rates were over twice those of males.

The short mean duration of illness makes the incidence rate and mortality rate approximately equal with an overall rate of 0·31 cases/million/year for the decade 1970–1979 in England and Wales.

Temporal distribution   The temporal distribution of cases within the decade is shown in Table 3 and shows an increase in the number of deaths towards the end of the decade, probably due to increased recognition and diagnosis of cases with time rather than a true increase in mortality rate.

Geographical distribution   The geographical distribution in England and Wales is shown in Fig 2. Analysis of cases by county (Fig. 3) shows a significant (χ^2 = 153·2; df = 52; p < 0·001) disparity between the mortality rates in individual counties. The county with the highest rate was Oxfordshire. This may be related to greater recognition of cases in an area in which there is particular interest in Creutzfeldt-Jakob disease. High rates were also observed, however, in Northumberland and Dorset. The rates were low in North and Central Wales, Somerset and in Lincolnshire, Northamptonshire and Hertfordshire. There was no obvious difference in rates between rural and urban counties, nor association with
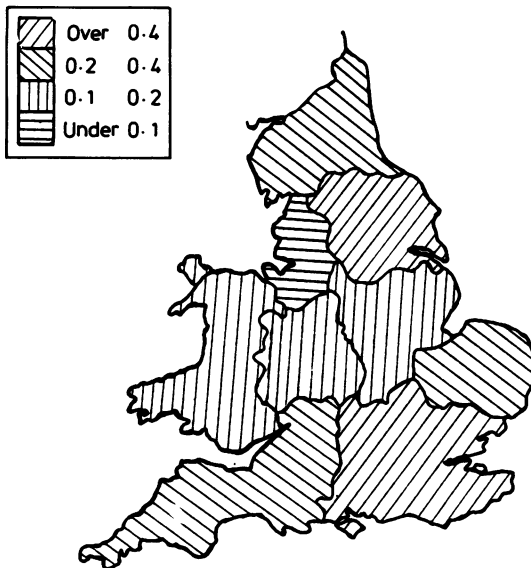
Fig 4   *Mortality rates of Creutzfeldt-Jakob disease by standard regions in England and Wales 1970–79.*

population density.

Analysis of cases by standard region (Fig. 4) confirms a significant geographical variation in mortality rates ($\chi^2 = 27{\cdot}1$; df $= 8$; p $< 0{\cdot}001$) and highlights the remarkably low incidence in the Northwest and low incidence rates in Merseyside and Manchester, despite the availability of good diagnostic services.

For rare diseases evidence of possible case-to-case transmission may be provided by the finding of "space-time" clustering of cases of disease.[8] If such transmission is occurring, cases which are close together in space might also be expected to have their onsets close in time, provided the incubation period (between infection and onset of symptoms) is short. For Creutzfeldt-Jakob disease, however, the incu-

bation period might be long, possibly several years. In such circumstances, if case-to-case transmission is occurring, associated cases might be expected to live close to each other but have their disease onsets separated by the incubation period of the disease (if the period of infectivity is short and close to the date of onset). Evidence for such "space-time" clustering was sought using the method of Knox.[8] All possible pairs of the 152 cases with known addresses were examined to determine the number that occurred within a defined time of each other and who were resident at the time of onset within a defined distance of each other. The choice of critical time and space distances is, to some extent, arbitrary, unless the means of transmission and incubation periods are known, so a variety of combinations were tried. The critical times selected were 1, 3 and 6 months and 1, 2, 3, 4 and 5 years. The critical distances were taken as 5, 10, 20 and 50 km. Table 4 shows the number of pairs of cases that were within these "critical" time and space intervals, together with the expected numbers of such pairs on the assumption of no space-time clustering.

In only one instance does the observed number of pairs shown in the table exceed the expected number by more than 2 standard deviations. This was for pairs of cases with dates of onset 3 to 6 months apart and resident within 50 km of each other. The only other notable excess is of pairs of cases resident within 20 km of each other and with onsets between 6 months and 3 years apart (number of pairs $= 178$, expected number $= 154{\cdot}0$; p $< 0{\cdot}05$). Given the number of possibilities examined, however, these apparent excesses may well be chance findings. Also, it is difficult to interpret space distances of this magnitude in terms of case-to-case transmission. There were no substantial changes to the findings if amyotrophic cases were excluded or if the analyses were restricted to sub-acute cases only or if the analyses were conducted using dates of death rather than dates of onset.

With the exception of familial cases, no contact between individual cases was discovered. An apparent

Table 4   *Space-time clustering: numbers of pairs of cases resident within 'critical' distances of each other and with dates of onset within 'critical' time period of each other*

Time interval between cases in pair†	Distance between place of residence of cases in pairs							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
Up to 1 mo	0	0·7	0	2·6	5	8·2	25	26·8
1 to 3 mo	1	1·0	4	3·6	8	11·5	36	37·7
3 mo to 6 mo	1	1·5	5	5·5	18	17·7	73*	57·9
6 mo to 1 y	5	2·9	14	10·9	41	34·7	124	113·7
1 y to 2 y	4	5·3	17	19·8	72	63·5	199	207·8
2 y to 3 y	5	4·7	22	17·5	65	55·8	206	182·8
3 y to 4 y	3	4·0	10	14·8	45	47·5	140	155·5
4 y to 5 y	5	3·4	13	12·6	37	40·2	118	131·6

*p 0·05.
†The critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1435 and 1830.

cluster of 7 cases in the Derby area, including patients dying in the 1960's, was extensively investigated by interviewing the relatives of six of the patients. No contact could be established between any of the cases despite their geographic proximity.

Occupation   Details of occupation were available in 86 patients, either from the death certificate or hospital notes, and in a further 56 patients details of the spouse's occupation was available. Of the 86 patients with known occupation, five could be classified as food handlers and five as employed in medically related professions. Of these two were hospital domestics and one a nurse, but no other hospital or laboratory staff were identified. The remaining patients had a wide variety of occupations and no particular type of job appeared to be associated with an increased risk of developing Creutzfeldt-Jakob disease. There was no obvious excess of occupations related to contact with sheep or sheep products.

Past medical history   Details of past medical history were available in 116 of the 158 patients and in 40 no significant past medical history was described. Of the remaining patients, 26 had had abdominal surgery and a further 7 patients other major surgery. Of particular interest were those patients who had undergone neurosurgery and one patient who had a cataract extraction. One patient had posterior fossa craniectomy on three separate occasions in the course of treatment of syringomyelia. Although these operations were carried out in a hospital to which a number of previous cases of Creutzfeldt-Jakob disease had been admitted, no association between the various cases could be established. A further patient underwent craniotomy in the course of treatment of trigeminal neuralgia two years prior to developing Creutzfeldt-Jakob disease but no contact with other cases could be established. One patient had a laminectomy and another a cataract extraction but without corneal transplantation. Thirty patients described important previous medical illness, including two patients treated with steriods, but no particular medical condition or infection was associated with an obviously increased risk of developing Creutzfeldt-Jakob disease.

Family history   Details of family history were available in only 98 cases and in six patients a positive family history of Creutzfeldt-Jakob disease was discovered. Four patients had a sibling who died of definite or probable Creutzfeldt-Jakob disease and the mother of one of these patients also died of the condition. Two further patients had a parent who died of possible Creutzfeldt-Jakob disease.

A patient of particular interest died in 1978, aged 75 years, of the amyotrophic form of Creutzfeldt-Jakob disease. Histology revealed changes typical of motor neuron disease, but, despite severe dementia at death and macroscopic evidence of cerebral atrophy, the histology of the cerebral cortex was remarkably normal. The patient's sister died in the 1960's of pathologically confirmed subacute Creutzfeldt-Jakob disease and a number of siblings were known to have died of presenile dementia.

Discussion

In contrast to previous studies in which the incidence has been found to be similar in males and females, a female excess has been found in this study, confined to deaths at age 65 years or older. The significance of this finding is uncertain, but it has continued in a case-control study of Creutzfeldt-Jakob disease currently being carried out in England and Wales.

The great majority of patients dying of Creutzfeldt-Jakob disease were aged between 50 and 75 years. This finding accords with that described in other studies.[5][6][9][11] The age-mortality curve (Fig. 1) is remarkably similar to that found for France[9] with the exception that in the French series the sharp drop in the mortality rate at older ages occurred after age 74 years rather than at 69 years as observed in the present series. This sharp decrease in mortality at older ages has been described in other studies[5][6][11] and is unexplained. Poor case ascertainment in the elderly is a possible explanation, though the clinical features of the disease are striking.

An alternative explanation is that Creutzfeldt-Jakob disease has a limited incubation period, albeit measured in decades, and that exposure to the agent early in life results in a maximal age at which the disease is likely to become manifest. There are few precedents for such a mechanism, however, as, in general, if incubation periods are long they are also highly variable.

The incidence of Creutzfeldt-Jakob disease varies between reports dependent on entry criteria, diagnostic criteria and method of case ascertainment. In a previous study of Creutzfeldt-Jakob disease in England and Wales[5] Matthews found an incidence of 0·09 cases/million/year but in this study only pathologically proven cases were included. In other retrospective studies the incidence rate in the USA has been reported as 0·25 cases/million/year,[6] in Chile 0·31[11] and in France 0·32.[9] The latter figure is very close to the incidence rate in this report and it is of note that both studies were carried out retrospectively in countries of similar population, using similar diagnostic criteria.

In epidemiological studies of urban areas, higher incidence rates have been discovered with figures of 1·8 cases/million/year in Brooklyn and Staten Island,[12] 0·93 in the city and district of Genoa,[13] 0·73 in Santiago[11] and 1·33 in densely populated areas of

Paris.[9] Brown *et al*[14] have postulated that there is a correlation between population density and the incidence rate of Creutzfeldt-Jakob disease based on both the disparity between the incidence rates in urban and rural France and in particular the relationship between incidence and population density within the Paris region. In our series no relationship was discovered between incidence by county and population density. Case finding artefacts due to increased recognition of cases in particular areas, perhaps due to contrasting availability of neurological services, cannot be excluded as an explanation of differing regional incidence rates, although this seems an unlikely explanation for the low rates of disease in the Northwest.

The conditions under which space-time clustering of a rare infectious disease might be expected to be observed are limited and thus the failure to find any convincing evidence of such clustering in the present series must be interpreted with caution. Firstly, if there is case-to-case transmission, clustering would only be expected, with the methods we have used (Table 4), if the incubation period was short, or was long but not very variable (an unlikely occurrence). Secondly, incomplete ascertainment may decrease the likelihood of finding space-time clustering. The possibility that this is a factor is suggested by the apparent increase in mortality rate over the study period (Table 3) which may well be due to an increased awareness of the condition among neurologists over the decade. Thirdly, if persons other than cases may transmit the infection, and such 'carriers' are common, clustering might not be expected. Conversely spurious clustering might be observed if case ascertainment changed differentially in different geographical areas, due, say, to the movement of neurologists with a special interest in the disease. Localised areas of high incidence have been described in England,[5] Czechoslovakia[15] and Hungary. Although it is of note that these were rural areas, it is impossible to judge the significance of these findings in the absence of background epidemiological data. In Oxfordshire, and other areas with a heightened awareness of the condition, detailed investigation failed to reveal convincing evidence of contact between individual cases. In a previous publication[10] definite contact between two individual cases was described.

An increased incidence of past surgical procedures has been described by Masters *et al*,[6] but other retrospective studies of Creutzfeldt-Jakob disease have failed to show an increased incidence of past medical or surgical illness. In the study in France[9] 8% of patients had some form of surgical procedure in the five years prior to developing Creutzfeldt-Jakob disease and in the present study, which was without temporal limits, 28% had a past history of major surgery. It is uncertain, however, whether such an incidence of past surgical procedures differs from the incidence in this age group in the general population and, as with other proposed risk factors, only a case-control study can assess the significance of putative risk factors discovered in descriptive epidemiological surveys. In such a case-control study in Japan[16] surgery in the five years before onset was discovered to be more common in cases than controls, although it is of note that this study involved only a small number of patients and used a "healthy" control group.

The overall familial incidence of 6% in this study contrasts with the estimated familial incidence of 15% in a review of the world-wide epidemiology of Creutzfeldt-Jakob disease.[6] In a comprehensive retrospective study in France, however, a 9% familial incidence was discovered, a figure comparable to this series. The low familial incidence may reflect either the difficulties of retrospectively obtaining an accurate family history or an artificially high familial incidence in relatively selected series due to extensive investigation of individual families.

Strong circumstantial evidence has been previously reported suggesting iatrogenic transmission of Creutzfeldt-Jakob disease by neurosurgery,[10] but this mechanism can be invoked to explain the development of Creutzfeldt-Jakob disease in only a small proportion of patients. Whether natural transmission occurs and if so by what means remains obscure. If contamination occurs at the time of minor dental or surgical procedures, it may only be by systematic investigation of individual cases that potential cross-contamination could be discovered.

Appendix

ICD codings and definitions.

8th ICD revision:
290.0	Senile dementia.	
290.1	Presenile dementia.	
331.9	Hereditary diseases of the striatopallidal system.	
333.9	Other hereditary and familial diseases of the nervous system (unspecified).	
342	Paralysis agitans.	
347.9	Other diseases of brain (unspecified).	
348	Motor neurone disease.	
781.7	Encephalopathy.	

References

1 Gibbs CJ, Gajdusek DC, Asher DM, Alpers HP, Beck E, Daniel PM, Matthews WB. Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science* 1985;**161**:388–9.

2 Hadlow WJ, Race RE, Kennedy RC, Eklund CM. Natural infection of sheep with scrapie virus. In: Prusiner SB and Hadlow WJ. eds. *Slow Transmissible Diseases of the Nervous System,* vol. 2. New York: Academic Press 1979:3–12.

3 Marsh RF, Hanson RP. On the origin of transmissible mink encephalopathy. In: Prusiner SB and Hadlow WJ. eds. *Slow Transmissible Diseases of the Nervous System,* vol. 1. New York: Academic Press 1979:441–60.

4 Alpers MP. Epidemiology and ecology of Kuru. In: Prusiner SB and Hadlow WJ. eds. *Slow Transmissible Diseases of the Nervous System,* vol. 1. New York: Academic Press 1979:67–90.

5 Matthews WB. Epidemiology of Creutzfeldt-Jakob disease in England and Wales. *J Neurol Neurosurg Psychiatry* 1985;**38**:210–3.

6 Masters CL, Harris JO, Gajdusek DC, Gibbs CJ, 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.

7 Will RG, Matthews WB. A retospective study of Creutzfeldt-Jakob disease in England and Wales 1970–1979: Clinical features. *J Neurol Neurosurg Psychiatry* 1984;**47**:134–40.

8 Knox EG. Epidemics of rare diseases. *Br Med Bull* 1971;**27**:43–7.

9 Brown P, Cathala F, Gajdusek DC. Creutzfeldt-Jakob disease in France 111: Epidemiological study of 170 patients dying in the decade 1968–1977. *Ann Neurol* 1979;**6**:438–46.

10 Will RG, Matthews WB. Evidence for case-to-case transmission of Creutzfeldt-Jakob disease. *J Neurol Neurosurg Psychiatry* 1982;**45**:235–8.

11 Galvez S, Masters C, Gajdusek DC. Descriptive epidemiology of Creutzfeldt-Jakob disease in Chile. *Arch Neurol* 1980;**37**:11–4.

12 Farmer PM, Kane WC, Hollenberg-Sher J. Incidence of Creutzfeldt-Jakob disease in Brooklyn and Staten Island. *N Engl J Med* 1978;**298**:283–4.

13 Tabaton M, Bugiani O, Mancardi GL, Leonardi A, Demartini I, Primavera A. Creutzfeldt-Jakob disease in the city and district of Genoa: estimated mortality rates in the six year period 1974–1979. *Ital J Neurol Sci* 1981;**2**:189–92.

14 Brown P, Cathala F, Sadowsky D. Correlation between population density and the frequency of Creutzfeldt-Jakob disease in France. *J Neurol Sci* 1983;**60**:169–76.

15 Mayer V, Orolin D, Mitrcua E. Cluster of Creutzfeldt-Jakob disease and presenile dementia. *Lancet* 1977; **2**:256.

16 Kondo K, Kuriowa Y. A case-control study of Creutzfeldt-Jakob disease: association with physical injuries. *Ann Neurol* 1982;**11**:377–81.