

Epidemiology of Creutzfeldt-Jakob disease in England and Wales

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SYNOPSIS Some aspects of the epidemiology of Creutzfeldt-Jakob disease in England and Wales in the decade 1964-73 were studied with the object of detecting evidence of natural transmission of this slow virus encephalopathy. Some geographical clustering and possibility of contact between cases was found.

Creutzfeldt-Jakob disease (CJD) was first transmitted to the chimpanzee in the laboratory in 1968 (Gibbs *et al.*, 1968) and has since been transmitted to other primates and recently to the cat (Gibbs and Gajdusek, 1973). The prolonged incubation period, the absence of inflammatory reaction or antibody formation, and the failure to detect an infective agent except by the induction of disease are characteristic of the slow virus spongiform encephalopathies. As with other diseases in this group, the possibility of natural transmission or of factors that might activate latent infection must be considered. With this in mind I studied the incidence of the disease in England and Wales during the decade 1964-73.

METHOD

Neuropathologists were asked to notify me of cases with histological verification diagnosed during this decade as CJD, subacute spongiform encephalopathy, or corticostriatal degeneration. Neurologists were asked to inform me of cases newly diagnosed on clinical grounds but these were included in the series only if histological confirmation was available later. To these were added cases, similarly verified, observed personally during this decade. Hospital notes were scrutinized and near relatives were asked to complete a questionnaire or were interviewed personally. Particular attention was paid to factors previously suggested as being of possible significance in the aetiology of the disease: head injury, stroke, cranial surgery (Nevin *et al.*, 1960), hepatic disease (Williamson *et al.*, 1973), febrile illness in the months preceding the onset, the consump-

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tion of brains (Bobowick *et al.*, 1973), and a positive family history (Bonduelle *et al.*, 1971) or family contact (Garzuly *et al.*, 1971). In addition information was sought on place of residence throughout life, foreign travel, and exposure to animals. In specific instances the question of possible contact between cases was explored.

RESULTS

Forty-six patients were identified in whom the disease began within the decade. Patients diagnosed in this country but whose disease had begun abroad were not included. Twelve patients had been either under my care or were seen personally. Using the 1971 census figures the annual incidence of confirmed CJD during this decade was 0.09 per million.

TABLE
YEAR OF ONSET OF CJD

	Year									
	1964	'65	'66	'67	'68	'69	'70	'71	'72	'73
Number of cases	4	1	4	1	7	4	6	7	4	8

Information from the hospital notes alone was available in 16 patients, while in 30 further details were obtained from relatives in the course of this study. Certain of the clinical aspects have been described elsewhere (Matthews, 1975). There were 30 women and 16 men. The mean age of

onset was 57 years with a range from 34 to 71 years. The year of onset is shown in the Table.

No patient had sustained a stroke or serious head injury but two had had intracranial surgery for trigeminal neuralgia two and 10 years before the onset of CJD respectively. A past history of jaundice was obtained in only one patient. In two patients the onset of the disease had been accompanied by diarrhoea and vomiting which did not persist for more than a few days. No pattern of ill-health in the year preceding the onset could be detected.

In three instances a sibling was reported to have had identical or similar disease but no histological or detailed clinical evidence could be obtained. One patient's first wife had died of a probably identical condition three years before he developed CJD but histological confirmation was not available.

Of the 30 patients on whom more detailed information was obtained eight had travelled beyond Europe but, in contrast, two had lived in the same house all their lives. Eighteen patients were living in large towns at the onset of CJD and the remainder in more rural areas. No consistent pattern could be detected in past medical history, inoculations, or occupation.

Fourteen patients were thought by their relatives never to have eaten brains while five were known to have done so. Two patients were thought not to have eaten any form of offal in adult life. Exposure to animals in the home was not universal, as within the memory of relatives seven patients had kept neither a cat nor a dog and only four had kept cage birds. Two patients had kept ferrets and one had been exposed to ferrets as a child and this unexpected finding is the subject of a separate investigation. There was no contact with live mink.

The geographical distribution was markedly uneven, only 10 patients living in the area to the west of 1° 40' W that includes the conurbations of Birmingham, Manchester, Liverpool, and Bristol. Several geographical clusters were detected, not related to areas of dense urban population. One concerned a small rural community in the Midlands (Fig. 1). In 1964 case 1, a woman of 46 years of age who had lived for 20 years at A in a village with a population of 1 500, developed CJD and died in hospital. In 1968 case 2, a woman of 34 years, living 40 miles away, also died of the disease. Her sister, with whom she often stayed, lived at B from 1957 to 1963, in a village with a population of 500, some 2 km from the home of case 1, and thereafter at C in the next village. Case 1 had often visited B and C and probably met case 2 but too pressing inquiry on this point was not thought desirable. In 1971 case 3, a man aged 54 years, died of CJD. From 1951 to 1966 he had lived at D and thereafter at E, in the same village where the sister of case 2 had lived. He was acquainted with case 2's brother-in-law and worked for the same firm but it is not known whether he ever met case 2 or her sister. CJD has been transmitted to the chimpanzee from case 2 (Roos *et al.*, 1973).

A second less well-documented cluster concerns five patients in an area of eastern England (Fig. 2). The patients at W, X, and Y had lived in the area at least since 1960. Their relatives were highly cooperative but it could not be established that there had been any contact between patients in this group. The area has no natural boundaries but in the administrative area the annual incidence of CJD for the decade was 1.3 per million, more than 10 times that for England and Wales.

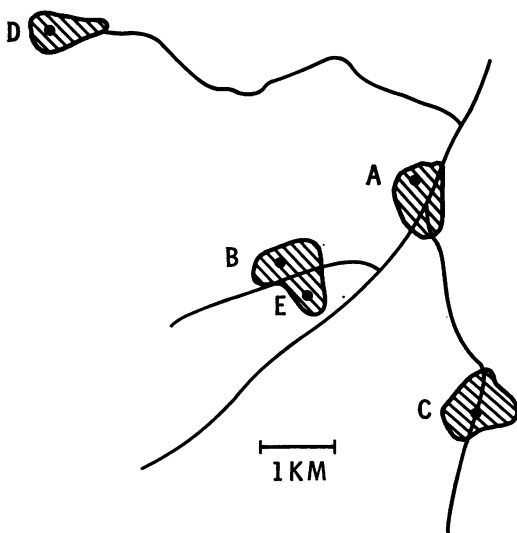


FIG. 1 Sketch map of cluster of cases of CJD in a rural area. Shading represents villages. The lettering is explained in the text.

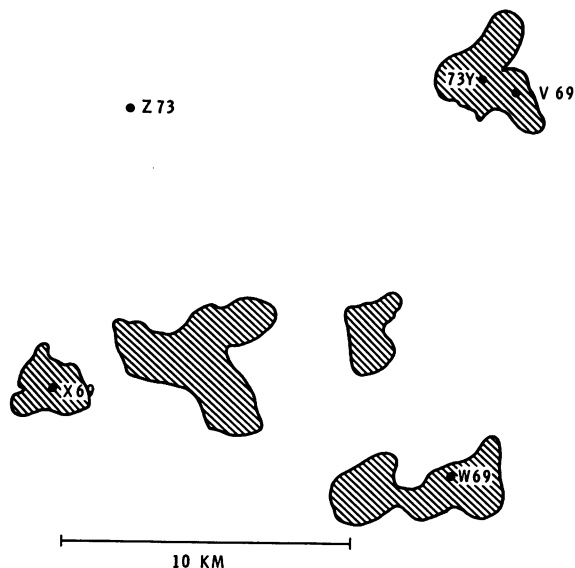


FIG. 2 Sketch map of distribution of cases of CJD in an area of eastern England. The figures indicate the year of onset of disease. Shading indicates built-up areas.

DISCUSSION

The four diseases classified as slow virus spongiform encephalopathies are scrapie in sheep, transmissible mink encephalopathy (TME), and kuru and CJD in man. All are artificially transmissible to a variety of hosts but natural transmission is less certain. Scrapie has been transmitted from sheep to goats and to sheep not naturally susceptible by close contact for several years (Brotherston *et al.*, 1968) but the part played by infection in natural scrapie is unknown. TME has appeared in explosive outbreaks in mink farms, apparently derived from some food source, possibly scrapie infected mutton (Hartsough and Burger, 1965). There is no evidence of transmission from mink to mink but all except breeding pairs are killed at six months so there is little opportunity for prolonged exposure or for the development of a disease with a long incubation period. There is strong evidence that ritual cannibalism played a part in the natural transmission of kuru (Gajdusek, 1972). CJD appears to have been transmitted accidentally from one person to another in a corneal graft (Duffy *et al.*, 1974). There has been one report of conjugal CJD, both partners developing the disease at the same time (Garzuly *et al.*, 1971). Familial CJD has been reported on a number of occasions (Bonduelle

et al., 1971) and it is known that the familial form is transmissible in the laboratory (Roos *et al.*, 1973). The reported pedigrees are compatible with dominant inheritance but also, of course, with contagion but no details of duration of contact between affected members have been given.

In the present study no claim can be made for complete discovery even of diagnosed cases. As can be seen from the Table there is some tendency for CJD to be diagnosed more frequently in recent years. The search for sources of infection or for possible precipitating factors was largely negative. An unexpectedly high incidence of previous craniotomy was also noted by Nevin *et al.* (1960) and with present knowledge of the transmissible nature of the disease might be regarded as a possible mode of entry of the agent rather than as precipitating the disease. A suggestion that eating hogs' brains might be important (Bobowick *et al.*, 1973) was not confirmed. The contact with ferrets in two patients may prove to be of interest. TME is transmissible to the white ferret, which may recover from the clinical disease, although the brain remains infective for mink (Marsh *et al.*, 1969).

It is remarkable that three cases of this rare disease occurred in a small community. One of these patients has been shown to have the trans-

missible form of CJD but it is intrinsically improbable that transmission could have been effected by any casual contact that may have occurred. The annual incidence calculated for the area in which the second illustrated group of patients lived is of doubtful validity because of the lack of natural boundaries. Kahana *et al.* (1974) found an annual incidence in most ethnic groups in Israel of from 0.4 to 1.9 per million but from their figures it can be calculated that the incidence of histologically verified CJD in Israelis not of Libyan origin was 0.38 per million. In the ethnic group of Libyan origin the annual incidence of verified cases was 26 per million. This high incidence was not due to familial cases but no details of possible contact have yet been published.

If CJD is naturally infectious at all it is likely that the incubation period is longer than the 18 months in the accidental transmission by corneal graft (Duffy *et al.*, 1974). The statement by Gibbs and Gajdusek (1973) that the incubation period is four to five months appeared in error (Gajdusek, 1974, personal communication). It is improbable that a disease as rare as CJD could be perpetuated solely by transmission from one overt case to another and the existence of non-fatal cases that might remain infective after recovery is at least a possibility.

ADDENDUM

Since the manuscript was submitted two further cases of CJD with onset in 1973 have been detected, both in the South-East of England.

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