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Creutzfeldt–Jakob disease

W. B. MATTHEWS
D.M., F.R.C.P.

Department of Clinical Neurology, Radcliffe Infirmary, Oxford

Summary

The laboratory transmission to animals of an apparently degenerative disease of the nervous system, Creutzfeldt–Jakob disease (CJD), is now well established. Important questions arising from this observation are the possibility of natural transmission or infectivity and the existence of other similarly transmissible diseases. Epidemiological studies have revealed some possible clusters of CJD and also an association with previous craniotomy, but there is no definite evidence of natural infection. A few instances have been reported of experimental CJD in animals following inoculation with material from Alzheimer's disease, but apart from this there is so far no evidence of transmission of any other form of degenerative nervous disease.

MOST textbooks of neurology include a gloomy chapter on 'degenerative diseases' in which are described a number of progressive disorders of unknown cause, with no effective treatment and an invariably fatal outcome. The discovery that two such 'degenerative' diseases of the CNS, kuru and Creutzfeldt–Jakob disease (CJD), were transmissible to laboratory animals was therefore naturally hailed as an important breakthrough, recognized by the award of the Nobel Prize for medicine to Dr Carlton Gajdusek for his energetic and fruitful research. Kuru is, however, a truly exotic disease, being confined, as far as is known, to certain tribes in the highlands of New Guinea. CJD probably occurs world-wide but is undoubtedly rare. The significance of these discoveries would be greatly enhanced if a connection could be established between these two diseases, which the great majority of doctors will never see, and more common degenerative afflictions – presenile dementia, Parkinson's disease and motor neurone disease, for example. Another aspect of particular importance to this meeting is the question whether CJD is indeed an infectious disease, i.e. whether it is naturally transmissible.

It is first necessary to describe the clinical features of CJD. It is predominantly a disease of middle age, the range in a personal survey being from 34 to 73 years (Matthews, 1975a) although the incidence in old age has not been systematically examined. Sometimes there is a relatively prolonged prodromal period, characterized by minor complaints of dizziness, lack of interest and mild depression, which, not unnaturally, is often diagnosed as due to psychiatric illness and, in any case, is impossible to recognize as CJD. More often, however, the onset is relatively abrupt with symptoms obviously due to organic nervous disease developing in the course of a few weeks or even a few days. These symptoms are extremely varied and include ataxia, focal weakness of the limbs, cortical visual loss, aphasia and visual hallucinations. In a typical case the patient rapidly becomes helpless. Speech is entirely lost at an early stage and swallowing is soon affected. The limbs become rigid or spastic to varying degrees. Involuntary movements of many different forms are common but do not resemble those of classical Parkinson's disease. In the course of a month or two the patient becomes mute and paralysed in the decerebrate or decorticate posture, probably blind and with frequent myoclonic jerking of the limbs and trunk and, less commonly, epileptic fits. Survival is merely a matter of nursing care and is fortunately not usually prolonged beyond about nine months from the onset of the first recognizable neurological symptoms.

In about 10% of cases in which the pathology is apparently the same the course of the disease is more prolonged with survival for a number of years. In these patients, the clinical features are somewhat different in that cortical blindness, complete loss of speech at an early stage and myoclonus are less frequent, and muscular wasting and fasciculation, often present to a slight extent in subacute cases, become predominant features (Matthews, 1975a). There has been a legitimate but essentially insoluble disagreement on whether the disease now known as Creutzfeldt–Jakob disease is in fact what was described by Creutzfeldt (1920) or Jakob (1921); in Creutzfeldt's case almost certainly not. Modern concepts of the clinical and pathological aspects are much more firmly based on the work of Nevin (Nevin *et al.*, 1960).

CJD is a disease of grey matter, the distinctive features being spongiform degeneration of neurones, neuronal loss and proliferation of fibrous astrocytes. All these changes may be found in other diseases but the combination in florid form involving cortex,

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thalamus, basal ganglia, cerebellum and spinal cord to varying degrees is highly characteristic. It should be noted that there is no trace of inflammatory reaction and that this is not a demyelinating disease. The other organs are usually normal but non-specific changes in the liver are occasionally seen.

The diagnosis of a fully developed case of the subacute form of CJD does not present much difficulty to anyone aware of the disease, but can obviously be mistaken for other cerebral catastrophes such as tumours. The CSF is normal. The EEG often contains stereotyped repetitive discharges that are suggestive of the diagnosis but not conclusive. A brain biopsy can clinch the diagnosis but is seldom necessary and is occasionally misleading. The more chronic forms may resemble Alzheimer's disease where myoclonus can also be prominent or, if muscle wasting is marked, motor neurone disease. In general, if the patient is able to talk at the stage when myoclonus is present the pathology will eventually be found to be that of Alzheimer's disease. Similarly, if the presentation is with muscular wasting of spinal origin, rather than with dementia, the pathological findings will resemble those of motor neurone disease rather than of CJD. To what extent these names are labels of convenience rather than indicating distinct entities has recently acquired some practical importance.

CJD has now been transmitted in the laboratory by a variety of means to a number of animal species. The first transmission was by intracerebral injection of brain material into a chimpanzee (Gibbs *et al.*, 1968). If transmission had proved possible only to the chimpanzee research could scarcely have continued, but transmission to other primates has proved successful and now, at last, also to more readily available laboratory animals, guinea-pigs (Manuelidis, 1975) and hamsters (Manuelidis *et al.*, 1977b). Transmission has been achieved by brain extracts injected systemically and by extracts from spleen and lymph nodes injected into the brain. The transmissible agent is therefore not confined to the CNS. Transmission has the characteristics of what has been called a 'slow virus infection'. It is certainly slow in that the incubation period is prolonged; 14 months for the first transmission of CJD to the chimpanzee (Gibbs *et al.*, 1968) and 8·5 years for kuru to the rhesus monkey (Gajdusek and Gibbs, 1972). Whether a virus in the ordinary sense of the word is involved and whether this can be characterized as an infection are perhaps debatable. Certainly no virus can be seen, no antibodies are produced and the transmissible agent is unpleasantly resistant to measures that destroy other micro-organisms. Of more immediate importance, however, is whether CJD is infective in the sense of being transmissible from an affected patient to a normal subject as distinct from the artificial methods of the laboratory.

It is worth looking first at the other transmissible spongiform encephalopathies that have been identified. Scrapie occurs naturally in sheep and opinion is still divided as to whether it is transmitted by contagion. There is no doubt that prolonged close contact will effect transmission (Brotherston *et al.*, 1968) but this is different from normal field conditions and the route of entry is not known. Transmission usually appears to be genetic or at least from one generation to the next. Transmissible mink encephalopathy (TME) occurs in explosive epidemics on domestic mink farms. There is no evidence of lateral transmission from one animal to another or of transmission to offspring. Infection by eating scrapie mutton has been suggested but remains unproved. Kuru was almost certainly transmitted by ritual cannibalism (Gajdusek, 1973) but from the description of these feasts it seems that the oral route was not the only possible means of infection, the conjunctiva and abrasions in the skin being other possibilities.

CJD is occasionally present in more than one member of a family but as with scrapie it is not entirely clear that this is the result of genetic transmission rather than vertical infection. Cannibalism is scarcely relevant but other dietary possibilities have been raised. There is a relatively high incidence of CJD among Libyan Jews in Israel (Kahana *et al.*, 1974). It has been suggested that this is due to the habit of eating sheep's eyeballs (Herzberg *et al.*, 1974). Some anecdotal evidence has been produced of consumption of sheep's brains being a means of infection (Alter *et al.*, 1975; Alter, Hoenig and Pratzon, 1977) but this seems unlikely and the rabies vaccine used in Egypt in a large number of subjects is prepared from sheep's brains and CJD does not develop following injection (Bell, 1977). Bobowick *et al.* (1973) found an unexpectedly high incidence of eating canned hog's brains in their patients but this habit was also prevalent in controls. Matthews (1975b) found that most patients never ate brains at all.

Certain other environmental factors seem more promising. In a number of studies (Nevin *et al.*, 1960; Matthews, 1975b) there has been a surprisingly high incidence of preceding craniotomy. This raises the possibility that intracranial surgery might activate the disease but also the more disturbing conjecture that it could provide a route of entry for an infective agent. In a personal study (Matthews, 1975b), since amplified by unpublished observations, there has been a curious association with ferrets. Of thirty-three cases of CJD confirmed by post-mortem and for whom information was available, three had kept ferrets and one man had been bitten

by a ferret 18 months before he developed CJD. The brain of this ferret has so far failed to transmit the disease to primates. A fourth patient for whom post-mortem was refused but in whom the diagnosis was highly probable had been so devoted to ferrets that he would allow them to roam around inside his shirt. He was frequently bitten but had disposed of his animals some 6 years before the onset of his disease. Ferrets can be infected with TME (Marsh *et al.*, 1969) but, until now, not with CJD; but an animal vector is certainly a possibility. It is not known how many of an equivalent control population would be found to have kept ferrets and obviously most patients with CJD have had no contact at all with these animals.

Of particular interest is the possibility of transmission from one person to another. There seems no reasonable doubt that this can occur in circumstances more resembling those of the laboratory than of everyday life. A patient who received a corneal graft from a subject later shown to have died of CJD developed the disease after an incubation period of 18 months (Duffy *et al.*, 1974). In experimental animals the cornea has been shown to be infective when implanted in the anterior chamber of the eye (Manuelidis *et al.*, 1977a). Even more disturbing is the report on two patients who developed CJD, one, 20 and the other, 16 months after depth electrodes had been used for recording the EEG (Bernoulli *et al.*, 1977). In each case two electrodes had been used previously in a patient known to have CJD some 3 months earilier. Sterilization had been attempted with formaldehyde vapour but it is known that 10% formal saline does not inactivate the CJD agent even after seven months' fixation (Gajdusek and Gibbs, 1976). Evidence of natural transmission is slight. There has been one report of conjugal CJD (Garzuly, Jellinger and Pilz, 1971), both spouses developing the disease simultaneously. In a personal survey a further conjugal pair was probably identified, but post-mortem was not carried out in one patient. Clustering has been reported (Matthews, 1975b) but the significance of this is impossible to interpret. In an unpublished observation two men with this rare disease were identified as having lived no more than 200 metres apart but details of possible contact could not be obtained.

The incidence of CJD cannot be established with any degree of accuracy. In its usual form it is so remarkable a disease that the post-mortem rate is likely to be high. In the decade from 1964 the annual incidence of cases confirmed by post-mortem in England and Wales was $0{\cdot}09/10^6$. This is certainly an underestimate but is probably not grossly inaccurate. It is difficult to see how such a rare disease could be maintained at this level simply by infection from one overt case to another. Nor is it at all probable that casual contact could be an effective mode of transmission. The idea that the infective agent is widespread but clinically latent and is activated to produce overt disease only in response to certain environmental events cannot be disproved but the largely negative results from the injection of brain homogenates from other diseases does not suggest that an active infective agent is present. If CJD is naturally transmissible the route of infection has not been identified.

There is at present considerable anxiety about the possibility of accidental infection in the laboratory or operating theatre. Traub, Gajdusek and Gibbs (1975) state that during 15 years of intensive investigation of transmissible encephalopathies there has been no instance of laboratory infection. They give a list of sensible precautions to take when dealing with post-mortem material. The infective agent has not been detected in excreta or blood and transmission has not been effected by simple contact. There appears to be no indication for barrier nursing of suspected cases or for special precautions in dealing with excreta or body fluids.

With one possible exception it does not so far seem probable that other degenerative diseases of the nervous system are caused by transmissible agents of the same character. Spongiform degeneration is sometimes seen in motor neurone disease (Brownell, Oppenheimer and Hughes, 1970) but this disease has not been transmitted nor has the more chronic form of CJD where muscle atrophy is prominent. Parkinson's disease may prove to be viral in origin but does not seem to be related to the spongiform encephalopathies. Even the endemic Parkinson's disease/dementia and amyotrophic lateral sclerosis in the island of Guam that seemed to be prime candidates have not been successfully transmitted. Alzheimer's disease is the common cause of presenile and senile dementia and its pathology is different from that of CJD. It is so common that some of the changes of Alzheimer's disease may be present in a patient who clearly died of CJD (Roos, Gajdusek and Gibbs, 1973). Traub, Gajdusek and Gibbs (1977) have reported the appearance of experimental CJD in primates following the injection of brain material from two patients in whom pathological examination showed the changes of Alzheimer's disease alone. In one of these patients the disease had been familial. These authors also report similar pathological findings in the experimental animal following inoculation with tissue from a single case of progressive supranuclear palsy. In neither of these examples was the disease from which the patient seemed to be suffering transmitted to the animal and there is room for speculation on whether the CJD agent had been activated by the other

cerebral disease. There is at present no indication that Alzheimer's disease itself is due to a transmissible agent.

A theory at present in favour is that all four spongiform encephalopathies, scrapie, TNE, kuru and CJD, are due to the same agent modified by the host. The range of animals to which transmission is possible, once thought to be distinctive for each disease, is showing increasing overlap. CJD has even been shown to occur in New Guinea (Traub *et al.*, 1977) and possibly the epidemic of kuru, which was formerly the commonest cause of death in the Fore people, was initiated by the consumption of brain and other tissue of a single case of this disease. The implications of these discoveries are in some respects less far reaching than had at first been supposed. For example, it is extremely improbable that the scrapie agent causes multiple sclerosis. Nevertheless, modes of thought about many forms of disease of the central nervous system have been radically altered. Although no hint of effective prevention or curative treatment has yet appeared it is no longer permissible tamely to accept causeless 'degeneration' as a satisfactory explanation of these disabling and fatal diseases.

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