Psychological Medicine, 1976, **6**, 343–345

EDITORIAL

Kuru

In 1957 Gajdusek & Zigas described the clinical features of a disease, kuru, hitherto unknown to Western medicine. Kuru was seen exclusively amongst the inhabitants of the Eastern Highlands of New Guinea. This neurological disease, with marked psychiatric features, was confined to members of the Fore people and their nearest neighbours, with whom they intermarry, and had at that time reached epidemic proportions, causing more than half of all recorded deaths in the region. It is believed that the first case appeared around the turn of the century.

'Kuru' is the Fore word for shivering or trembling as with cold or fear and a fine tremor is one of the diagnostic signs of the disease. Clinically kuru has an insidious onset, with ataxia and disturbance of balance. These disturbances are often first noted by a relative before the patient becomes aware of them. Many patients recall having headaches before the first signs of the disease appear. Ataxia becomes progressively more severe and is soon accompanied by a fine tremor involving the trunk, head and extremities. Within a few months the patient is no longer able to walk or stand without support. Speech slowly becomes unintelligible and in the later stages of the disease patients are quite unable to talk. There is a tendency to jerky eye movements but no true nystagmus. The patients show a blunting of their personality and an emotional lability. Gajdusek does not regard dementia as a prominent feature of kuru, though Hornabrook (1968) considers that it develops in the later stages of the disease. Dysphagia develops after a time and this contributes to the severe wasting seen in the last stages of the disease. The course taken by the illness is stereotyped, with little variation between different patients and there is no response to any form of treatment. Death usually occurs partly from starvation, partly from decubitus ulceration within 9–24 months after the onset of clinical signs, but cases of only 3–6 months duration have been recorded. Convulsions, paralysis and sensory impairment do not occur, although pyramidal signs may sometimes be present during the terminal stage. When the disease was first described, the majority of cases occurred amongst young women and children of both sexes, but in the course of the last 15 years the incidence in children has become lower, more cases are observed in adults and the number of cases seen is decreasing rapidly.

Abnormalities in the urine, blood and CSF have not been found, nor have antibodies to any of the known encephalitides been demonstrated. Histopathological studies by, amongst others, Klatzo *et al.* (1959), Fowler & Robertson (1959), Beck & Daniel (1965), Beck *et al.* (1969) showed that the condition was a subacute degeneration of the central nervous system. In the cerebral cortex many nerve cells are lost and others show degeneration, the grey matter is spongy and there is proliferation and hypertrophy of fibrous astrocytes and some microglial reaction. The limbic cortex, i.e. cingular, insular and parahippocampal cortex, is particularly severely affected while elsewhere areas of the cortex may appear essentially normal and show a well-preserved cytoarchitecture. Alzheimer's neurofibrillary tangles and senile plaques have not been observed. Large vacuoles are seen in many of the big neurons in the striatum and an increased amount of neurosecretory material is found in the tuber cinereum; the latter pointing to some nerve fibre degeneration in the hypothalamo-neurohypophysial tract. There is no inflammatory reaction and the cerebral white matter is not demyelinated. Sharply demyelinated plaques, such as are seen in disseminated sclerosis, have never been observed.

The severest changes, by far, are found in the cerebellum, which shows atrophy of its foliae, particularly noticeable in the phylogenetically old vermis and flocculo-nodular lobe. Microscopically there is a severe loss of granule cells, degeneration of Purkinje cells and a dense fibrillary gliosis; the molecular layer contains numbers of microglial cells in all stages of phagocytic activity. Another feature in most cases is the presence of amyloid plaques throughout the cerebellar cortex and the subcortical white matter. These plaques resemble the so-called 'burned-out' stage of the senile plaque (Terry & Wiśniewski, 1970; Wiśniewski & Terry, 1973) but lack the contingent of degenerating

neurites which are typical of the 'classical or mature' senile plaque (Krücke *et al.*, 1973). The brainstem nuclei which have afferent cerebellar connexions such as the pontine nuclei, inferior olives and medial vestibular nuclei, show degenerative changes. The cortico-spinal tracts are degenerated in about half the cases. Like the clinical signs, the histopathological changes are stereotyped and the distribution of the lesions within the limbic cortex, striatum and hypothalamus as well as those within the cerebellum and its connexions is essentially the same in all cases.

The pathological changes that are found in the nervous system explain most of the signs seen in the disease and some of the symptoms. The severe degeneration of the cerebellum accounts for the ataxia and tremor, the degenerated vestibular nucleus for the disturbance of balance, while the degeneration of the cerebral cortex accounts for the speech defects, the emotional and personality changes and for the dementia, when this is present.

The pathogenesis of kuru remained an enigma until Hadlow in 1959 made a suggestion that was to have important results. He was impressed by the similarities in the histological changes in the brains of sheep with natural scrapie and those in the brains of patients with kuru. Since it had been found to be possible to transmit scrapie from affected sheep to normal sheep and to goats by inoculation Hadlow suggested that it might be worth while to attempt to transmit kuru to primates. In 1963, Gajdusek took up Hadlow's suggestion and inoculated chimpanzees with brain material from cases of kuru. After a prolonged incubation period the inoculated animals developed a kuru-like syndrome (Gajdusek *et al.*, 1966). Clinically the animal becomes withdrawn and lethargic and develops increasing signs of ataxia which lead to frequent falls and stumbles. Occasionally shivering-like tremors are seen. Terminally the animal is no longer able to sit up without support and has to be hand-fed; its facial expression becomes vacant and there is usually some visual impairment. To date the duration of the disease from the appearance of the first clinical signs to a moribund stage ranges between 1 and 15 months, the incubation time between 10 and 39 months. Since these early experiments kuru has been transmitted to chimpanzees from 11 different patients; it has also been transmitted serially through chimpanzees up to the fifth passage, with incubation times decreasing to an average of 12 months. Later, transmission to New World and rhesus monkeys was achieved.

The inoculum has been prepared from brain, from kidney, spleen or liver, it has been given intracerebrally or by a peripheral route, stored at -70 °C for 2 years, diluted as high as 10^{-7}, filtered through a 220 nm gradocol membrane and heated to 85 °C for 30 min; finally it has been prepared from long-maintained explant cultures of kuru brain tissue. All these varieties of inoculum have induced the experimental disease, which throughout has remained clinically and pathologically remarkably constant (Lampert *et al.*, 1972). Although much work has been done in trying to discover the nature of the transmissible agent no virus or virus-like structure has been identified with the electron microscope.

It seems possible that the disease was originally spread by inoculation, for at the time of its highest incidence there were ceremonies in which ritual cannibalism played a part and the tissues of those dead of kuru were handled by the living. Thus the opportunity of 'self-inoculation' through cuts and abrasions was great.

Attempts have been made to find out whether other degenerative diseases of the brain associated with mental abnormalities can be transmitted to animals by inoculation and material from cases of Alzheimer's and Pick's disease and from Creutzfeldt-Jakob disease have been used by Dr Gajdusek. So far, only Creutzfeldt-Jakob disease has been shown to be transmissible (Gibbs *et al.*, 1968), and it is interesting that the histopathology of this condition closely resembles that of experimental kuru (Beck *et al.*, 1969). It may be noticed that Klatzo *et al.* (1959) originally likened the histopathology of kuru to that of Creutzfeldt-Jakob disease.

Recent experiments suggest that Creutzfeldt-Jakob disease may be transmissible to mice and it is hoped that progress in elucidating the basic causes of these degenerative diseases of the brain, which are associated with such distressing mental changes, will advance more rapidly than it has done in the past, when the only animal available for experimental work was the rare and expensive primate.

ELISABETH BECK
PETER DANIEL

REFERENCES

Beck, E. & Daniel, P. M. (1965). Kuru and scrapie compared: are they examples of system degeneration? In *Slow, Latent and Temperate Virus Infections*, pp. 85–93. National Institute of Neurological Diseases and Blindness Monograph, no. 2 (U.S. Department of Health, Education and Welfare).

Beck, E., Daniel, P. M., Alpers, M., Gajdusek, D. C. & Gibbs, C. J. Jr. (1969). Neuropathological comparisons of experimental kuru in chimpanzees with human kuru. In *Pathogenesis and Etiology of Demyelinating Diseases*. Add. ad *International Archives of Allergy, and Applied Immunology (Basel)* **36**, 553–562.

Fowler, M. & Robertson, E. G. (1959). Observations on kuru: pathological features in five cases. *Australian Annals of Medicine* **8**, 16–26.

Gajdusek, D. C., Gibbs, C. J. Jr. & Alpers, M. (1966). Experimental transmission of a kuru-like syndrome to chimpanzees. *Nature, London* **209**, 794–796.

Gajdusek, D. C. & Zigas, V. (1957). Degenerative disease of the central nervous system in New Guinea: the endemic appearance of kuru in the native population. *New England Journal of Medicine* **257**, 974–978.

Gibbs, C. J. Jr., Gajdusek, D. C., Asher, D. M., Alpers, M. P., Beck, E., Daniel, P. M. & Matthews, W. B. (1968). Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science* **161**, 388–389.

Hadlow, W. J. (1959). Scrapie and kuru. *Lancet* ii, 289.

Hornabrook, R. W. (1968). Kuru: a subacute cerebellar degeneration. The natural history and clinical features. *Brain* **91**, 53–74.

Klatzo, I., Gajdusek, D. C. & Zigas, V. (1959). Pathology of kuru. *Laboratory Investigation (New York)* **8**, 799–847.

Krucke, W., Beck, E. & Vitzthum, H. G. (1973). Creutzfeldt-Jakob disease: some unusual morphological features reminiscent of kuru. *Zeitschrift für Neurologie* **206**, 1–24.

Lampert, P. W., Gajdusek, D. C. & Gibbs, C. J. Jr. (1972). Subacute spongiform virus encephalopathies. Scrapie, kuru and Creutzfeldt-Jakob disease: a review. *American Journal of Pathology* **68**, 626–646.

Terry, R. D. & Wiśniewski, H. (1970). The ultrastructure of the neurofibrillary tangle and the senile plaque. In G. E. W. Wolstenholme & M. O'Connor (eds.), *Alzheimer's Disease and Related Conditions*, pp. 145–165. Churchill: London

Wiśniewski, H. M. & Terry, R. D. (1973). Re-examination of the pathogenesis of the senile plaque. In H. M. Zimmerman (ed.), *Progress in Neuropathology*, vol. II, pp. 1–26. New York and London: Grune & Stratton.