

EDITORIAL

Iatrogenic transmission of Creutzfeldt-Jakob disease¹

Creutzfeldt-Jakob disease is a rare progressive neurological disorder which is eventually fatal. Attention has recently been focused upon the iatrogenic transmission of this disease by four published reports of patients developing Creutzfeldt-Jakob disease associated with the administration of human growth hormone preparations originally prepared from human cadaver pituitaries.

Characterized clinically by ataxia, usually by dementia, and often by myoclonic movements, Creutzfeldt-Jakob disease progresses to a stuporose state and death within a few months of onset (Masters & Richardson, 1978). The disease has an incidence of approximately 1 per million of the population per year (Brown *et al.* 1985), and mainly affects those over 50 years of age; cases under 30 years old are very rare (Brown *et al.* 1985). Pathologically, Creutzfeldt-Jakob disease exhibits a characteristic histologic appearance of spongiform change in the neuropil of the cerebral cortex. Electron microscopy has shown that the spongiform change is due to the swelling and vacuolation of dendrites (Lampert *et al.* 1971, Gray, 1986). In patients surviving for more than 6 months with the disease, there is usually widespread gliosis of the cortex, basal ganglia and cerebellum with varying degrees of cerebral and cerebellar atrophy (Masters & Richardson, 1978).

The transmissible nature of Creutzfeldt-Jakob disease became clear in 1968 when cerebral biopsy tissue from a patient with the disease was injected into the brain of a chimpanzee (Gibbs *et al.* 1968). After a period of 13 months, the animal developed the clinical and pathological signs of Creutzfeldt-Jakob disease. Although the identity of the transmissible agent was unknown at that time, it was soon recognized that Creutzfeldt-Jakob disease in man had many similarities to scrapie in sheep and that both diseases were due to unconventional agents or 'slow viruses'. The unconventional agent associated with scrapie has been much more extensively characterized than has the agent causing Creutzfeldt-Jakob disease (Kimberlin, 1986). However, neither the exact nature of the infective agents nor the mechanisms by which they cause scrapie or Creutzfeldt-Jakob disease has been fully elucidated. A proteinaceous infectious particle (prion) has been isolated from scrapie and from Creutzfeldt-Jakob infected brains (Prusiner, 1982; Prusiner *et al.* 1987). The protein is a glycoprotein with an apparent molecular weight of 27000-30000 daltons and is designated PrP 27-30 (Prusiner *et al.* 1987). This protein is a major constituent of the minute scrapie-associated fibrils (SAF), 4-6 nm in diameter, which can be isolated from scrapie and Creutzfeldt-Jakob infected brains, but not from normal brain (Merz *et al.* 1981, 1983; Carp *et al.* 1985). Coded by a single gene, PrP 27-30 is present in several species and is expressed in uninfected brains (Kimberlin, 1986). This normal protein seems to be modified in scrapie infected brains, so that it accumulates as scrapie-associated fibrils and as amyloid deposits.

Although injection of preparations of scrapie-associated fibrils will transmit the disease, it is still not certain that the fibrils themselves are the infectious agent in scrapie or whether the agent itself is merely adherent to the fibrils (Kimberlin, 1986). It does appear from chemical studies that the scrapie and Creutzfeldt-Jakob agents do not contain significant amounts of DNA or RNAs as both agents are resistant to nucleases, ultraviolet light irradiation and other procedures which inactivate DNA and RNA. The protein nature of the scrapie agent is emphasized by its susceptibility to processes which inactivate proteins, such as the hydrolytic activity of trypsin (Griffin, 1985). However, it has been shown in scrapie that the infectious agent can undergo mutation and that it interacts with host genes; such observations suggest that there may be a small amount of nucleic

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acid associated with scrapie and possibly the Creutzfeldt-Jakob infectious agents (Kimberlin, 1986).

The concept of prion infections has been extended to include a group of six rare diseases (Griffin, 1985, Prusiner *et al.* 1987). Three of these diseases occur in animals viz: scrapie, transmissible mink encephalopathy, and chronic wasting disease of deer and elk. Another three diseases occur in man, viz. kuru, Creutzfeldt-Jakob disease and Gerstmann-Sträussler syndrome. All six diseases affect the central nervous system, have prolonged incubation periods, are inevitably fatal and are characterized by spongiform change in the brain.

The mode of natural transmission of Creutzfeldt-Jakob disease is unclear. With an incidence of 1 per million (Brown *et al.* 1985) the disease could scarcely be perpetuated solely by transmission from overt cases. It is, however, possible that the agent is widespread but only rarely pathogenic (Matthews, 1986). Some clusters of cases have been recorded, but it is not clear how the disease could be transmitted by social contact (Will & Matthews 1982). A 6–15% familial incidence has been suggested, but doubt has been cast upon these figures through the inclusion of unproven cases (Matthews, 1986).

Although the origins of the infection in sporadic cases of Creutzfeldt-Jakob disease remain obscure, different routes of experimental transmission of this disease and more especially of scrapie have been extensively investigated. In addition to intracerebral injection, both scrapie and Creutzfeldt-Jakob disease can be transmitted by oral routes and by peripheral injections (Kimberlin, 1986). Intramuscular injection of the scrapie agent is followed by invasion of the central nervous system from lymphoreticular sites of agent replication. In one scrapie model, spread of the agent occurs along autonomic nerves to the thoracic spinal cord and thence to other parts of the central nervous system (Kimberlin, 1986). Other studies suggest that the scrapie agent spreads in neurons. There is a close relationship between the presence of replicating scrapie agent and the vacuolated spongiform change in the cerebral cortex (Kimberlin, 1986).

A number of cases of suspected iatrogenic transmission of Creutzfeldt-Jakob disease were recorded before 1985 (Will & Matthews, 1982). In one case, a 55 year-old woman died from the disease 18 months after receiving a corneal transplant from a 55 year-old man who was later found to have died from Creutzfeldt-Jakob disease (Duffy *et al.* 1974). Two further cases of intracerebral transmission of the disease were reported by Bernoulli *et al.* (1977). Transmission in these cases apparently occurred when intracerebral electrodes, previously used in the investigation of a patient with Creutzfeldt-Jakob disease, were temporarily inserted into the brains of two epileptic patients. Although the electrodes had been sterilized by conventional means, this proved to be ineffective for the elimination of the infectious agent. A number of other reports have appeared in which transmission of Creutzfeldt-Jakob disease has been suspected, as in the case of a 28 year-old woman who developed Creutzfeldt-Jakob disease following a neurosurgical operation which included the grafting of commercially prepared dura mater (MMWR, 1987)

In early 1985 the distribution of human growth hormone for replacement therapy of growth hormone deficient children was halted by authorities in the United States and in Britain following reports that patients had died of Creutzfeldt-Jakob disease following the administration of human growth hormone. The British case (Powell-Jackson *et al.* 1985; Weller *et al.* 1986) was a young woman, born in 1962, who at the age of 2 years had a neurosurgical operation for the removal of craniopharyngioma. She subsequently received human growth hormone extracted from post mortem human pituitary glands for a period of 4 years between 1972 and 1976. In March 1984, at the age of 22 years, she exhibited clumsiness and unsteadiness while walking. By July of the same year she had developed a mild paraparesis and a left extensor plantar response. No abnormal investigations were noted at this time but during the next few months her behaviour became increasingly childish, demanding and disinhibited. She then developed a slurring dysarthria, disordered eye movements and showed titubation and severe ataxia of the limbs and trunk. There was general intellectual deterioration although no myoclonic movements were observed. A diagnosis of Creutzfeldt-Jakob disease was made despite the absence of myoclonic movements. The patient continued to deteriorate and by December 1984 she was mute and unresponsive; she died

in February 1985. The diagnosis of Creutzfeldt-Jakob disease was confirmed by the presence of spongiform change detected histologically in layers 2 and 3 throughout the frontal cortex and in the insula of both cerebral hemispheres. There was neuronal loss with proliferation of reactive astrocytes, particularly in layers 5 and 6 of the frontal cortex. Spongiform change and gliosis were also present in the putamen, globus pallidus, caudate nucleus and thalamus. Pronounced cerebellar cortical atrophy was observed with loss of granule cells but with relative preservation of Purkinje cells. No spongiform change was seen in the cerebellum but there was extensive gliosis (Weller *et al.* 1986).

The two cases of Creutzfeldt-Jakob disease in the United States, which had originally precipitated the ban on cadaver-pituitary derived human growth hormone administration, were both in their twenties and neither had had intracranial surgery. One patient was a man aged 23 who died 18 months after the onset of clinical signs (Gibbs *et al.* 1985). A diagnosis of Creutzfeldt-Jakob disease was made from the histological finding of spongiform change in the brain and by the isolation of scrapie-associated fibrils and their constituent protein PrP 27–30 from post mortem brain tissue. The case of Koch *et al.* (1985) was a 20 year-old man who had received human growth hormone preparations between 1966–1980. He developed signs of Creutzfeldt-Jakob disease in May 1984 and died 6 months later. At post mortem he showed the characteristic spongiform change of Creutzfeldt-Jakob disease throughout the cerebral cortex, basal ganglia and molecular layer of the cerebellar cortex but with little gliosis or neuronal loss. A further case of Creutzfeldt-Jakob disease in the United States occurred in a 32 year-old man who received growth hormone preparations between 1963 and 1969 (Tintner *et al.* 1986). Clinically, this patient was rather atypical as he exhibited little dementia but gross cerebellar signs. The disease was confirmed by pathology.

There is convincing argument in favour of cadaver-derived pituitary human growth hormone being the source of infection in the three American and one British patients treated with human growth hormone. Of the 3000 reported cases of Creutzfeldt-Jakob disease, only nine were under the age of 30 years (Brown *et al.* 1985). There are now 10000 people in the USA and 2000 in Britain who have received human growth hormone treatment and all are under 40 years of age (Brown *et al.* 1985; Preece, 1986). The probability of three cases of Creutzfeldt-Jakob disease occurring by chance in the American group of patients has been calculated as $1:10^{12}$ (Brown *et al.* 1985). It has proved difficult to predict how many more cases of the disease will occur in the future, but it is hoped that the purification steps used since 1980 in the preparation of human growth hormone from cadaver pituitaries (Taylor *et al.* 1985) will have eliminated the infectious agent.

Since the original four cases were published, there have been unpublished reports of three definite cases of Creutzfeldt-Jakob disease associated with human growth hormone preparations and one suspicious case. Of the three cases that show pathological evidence of Creutzfeldt-Jakob disease, one died at the end of 1986 in New Zealand having received an American batch of growth hormone in the past. Another two deaths occurred in the United States in 1987. One was a male in his mid-twenties who presented with dysarthria and ataxia and not the classical clinical picture of Creutzfeldt-Jakob disease. A female patient who had received growth hormone preparation also died from a non-neurological illness and bronchopneumonia but pathological examination of her brain revealed the changes of spongiform encephalopathy compatible with Creutzfeldt-Jakob disease.

The atypical presentation of Creutzfeldt-Jakob disease and its long incubation period in some of the patients, especially those reported by Powell Jackson *et al.* (1985) and by Tintner *et al.* (1986), may well be due to the peripheral route of infection (Kimberlin, 1986). It does mean, however, that the clinical awareness of Creutzfeldt-Jakob disease, particularly in this group, needs to be widened.

Apart from the obvious concern regarding the transmission of Creutzfeldt-Jakob disease to patients who have received human growth hormone preparations, there are also the problems raised by withdrawing growth hormone preparations for hormone-deprived children (Preece, 1986). However, a safe non-immunogenic human pituitary growth hormone with high activity and produced by recombinant DNA techniques should soon be widely available.

Since the first reports of iatrogenic transmission of Creutzfeldt-Jakob disease, precautions for handling tissues and body products from patients with the disease have been instituted (Rosenberg *et al.* 1986). Avoidance of skin contact with infectious materials is recommended and sterilization procedures for tissue and contaminated material include steam autoclaving for one hour at 132 °C and immersion in 1N sodium hydroxide for 1 hour at room temperature. Formalin fixation does not destroy the Creutzfeldt-Jakob disease agent, as transmission occurs following intracerebral injection of formalin-fixed brain material into non-human primates (Brown, 1986). It should be noted, however, that no medical staff, laboratory staff or autopsy technicians who are most likely to be exposed to the tissues and body products of patients with Creutzfeldt-Jakob disease have contracted the disease (Rosenberg *et al.* 1986).

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REFERENCES

- Bernoulli, C., Siegfried, J., Baumgartner, G., Regli, F., Rabinowicz, T., Gajdusek, D. C. & Gibbs, G. J. Jr. (1977). Danger of accidental person-to-person transmission of Creutzfeldt-Jakob disease by surgery. *Lancet* **1**, 478-479.
- Brown, P., Gajdusek, D. C., Gibbs, C. J. & Asher, D. M. (1985). Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. *New England Journal of Medicine* **313**, 728-730.
- Brown, P., Gibbs, J. C., Gajdusek, D. C., Cathala, F., LaBauge, R. (1986). Transmission of Creutzfeldt-Jakob disease from formalin-fixed paraffin-embedded human brain tissue. *New England Journal of Medicine* **315**, 1614-1615.
- Carp, R. I., Merz, P. A., Kascsak, R. I., Merz, G. S. & Wisniewski, H.M. (1985). Nature of the scrapie agent: current status of facts and hypothesis. *Journal of General Virology* **66**, 1357-1368.
- Duffy, P., Wolf, J., Collins, G., DeVoe, A. G., Streeten, B. & Cowen, D. (1974). Possible person-to-person transmission of Creutzfeldt-Jakob disease. *New England Journal of Medicine* **290**, 692-693.
- Gibbs, C. J., 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.
- Gibbs, C. J. Jr., Joy, A., Heffner, R., Franko, M., Miyazaki, M., Asher, D. M., Parisi, J. E., Brown, P. W & Gajdusek, D. C. (1985). Clinical and pathological features and laboratory confirmation of Creutzfeldt-Jakob disease in a recipient of pituitary derived human growth hormone. *New England Journal of Medicine* **313**, 734-738.
- Gray, E. C. (1986). Spongiform encephalopathy: a neurocytologist's viewpoint with a note on Alzheimer's disease. *Neuropathology and Applied Neurobiology* **12**, 149-172.
- Griffin, B. E. (1985). Unconventional viruses or prions? *British Medical Journal* **290**, 1765-1766.
- Kimberlin, R. H. (1986). Scrapie: How much do we really understand? *Neuropathology and Applied Neurobiology* **12**, 131-147.
- Koch, T. K., Berg, B. O., DeArmond, S. J., Gravina, R. F. (1985). Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism: possible relation to the administration of cadaveric human growth hormone. *New England Journal of Medicine* **313**, 731-733.
- Lampert, P. W., Gajdusek, D. C. & Gibbs, C. J. (1971). Experimental spongiform encephalopathy (Creutzfeldt-Jakob disease) in chimpanzees. Electron microscope studies. *Journal of Neuropathology and Experimental Neurology* **30**, 20-32.
- Masters, C. L., & Richardson, E. P. Jr. (1978). Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease). The nature and progression of spongiform change. *Brain* **101**, 333-344.
- Matthews, W. B. (1986). Unconventional virus infections and neurological disease. *Neuropathology and Applied Neurobiology* **12**, 111-116.
- Merz, P. A., Somerville, R. A., Wisniewski, H.M., Iqbal, K. (1981). Abnormal fibrils from scrapie infected brains. *Acta Neuropathologica* **83**, 63-74.
- Merz, P. A., Somerville, R. A., Wisniewski, H. M., Mannelidis, L. & Mannelidis, E. E. (1983). Scrapie-associated fibrils in Creutzfeldt-Jakob disease. *Nature* **306**, 474-476.
- MMWR (1987). Leads from the MMWR. Rapidly progressive dementia in a patient who received a cadaveric dura mater graft. *Journal of the American Medical Association* **257**, 1306-1037.
- Powell-Jackson, J., Weller, R. O., Kennedy, P., Preece, M. A., Whitecombe, E. M., Newsom-Davis, J. (1985). Creutzfeldt-Jakob disease after administration of human growth hormone. *Lancet* **ii** 244-246.
- Preece, M. A. (1986). Creutzfeldt-Jakob disease: implications for growth hormone deficient children. *Neuropathology and Applied Neurobiology* **12**, 509-515.
- Prusiner, S. B. (1982). Novel proteinaceous infectious particles cause scrapie. *Science* **216**, 136-144.
- Prusiner, S. B., Gabizon, R., McKinley, M. P. (1987). On the biology of prions. *Acta Neuropathologica* **72**, 299-314.
- Rosenberg, R. N., White III C. L., Brown, P., Gajdusek, C., Volpe, J. J., Posner, J. & Dyck, P. J. (1986). Precautions in handling tissues, fluids and other contaminated materials from patients with documented or suspected Creutzfeldt-Jakob disease. Committee on Health care issues ANA. *Annals of Neurology* **19**, 75-77.
- Taylor, D. M., Dickinson, A. C., Fraser, H., Robertson, P. A., Salacinski, P. R. & Lowry, P. J. (1985). Preparation of growth hormone free from contamination from unconventional slow viruses. *Lancet* **ii**, 260-262.
- Tintner, R., Brown, P., Hedley-White, E. T., Rappaport, E. B., Piccado, C. P. & Gajdusek, D. C. (1986). Neuropathological verification of Creutzfeldt-Jakob disease in the exhumed American recipient of human pituitary growth hormone: epidemiologic and pathogenetic implications. *Neurology* **36**, 932-936.
- Weller, R. O., Steart, P. V. & Powell-Jackson, J. D. (1986). Pathology of Creutzfeldt-Jakob disease associated with pituitary derived human growth hormone administration. *Neuropathology and Applied Neurobiology* **12**, 117-129.
- Will, R. G. & Matthews, W. B. (1982). Evidence of case-to-case transmission of Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery and Psychiatry* **45**, 235-238.