

The human prion disease hypothesis does not justify the origin of bovine spongiform encephalopathy

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The human prion disease hypothesis is based on the authors' declaration that the large-scale import by UK of crushed/whole bones and carcass parts containing soft tissue of mammalian origin, from India, Pakistan and Bangladesh, in the 1960s, ended up under poor control and regulatory conditions as animal feed.^[1] The authors declare that the half-burnt bodies of deceased Hindus that floated down the river Ganges were a source of human remains that were utilized together with animal bones by the processing mills for animal feed in the UK. According to Colchesters, these partly cremated bodies were infected with the human transmissible spongiform encephalopathy (TSE) called Creutzfeldt-Jacob disease (CJD), thereby becoming the root cause of the BSE epidemic in the UK. The Colchester hypothesis is partly based on the book by Dr. Alley, a physical anthropologist, who has in the meanwhile disassociated himself with this hypothesis, categorically mentioning that the information in his book and some of the personal discussion Colchesters had with him had been misquoted.^[2] In our view, the human prion disease hypothesis is implausible since no cases of bovine spongiform encephalopathy (BSE) have been reported in India to date, this indicating a low level of TSE in the region. Even suspecting that surveillance for BSE in India may

not be perfect, BSE epidemics have only occurred in those countries where there has been intensive farming with recycling of waste cattle tissue back to cattle in meat and bone meal. Such a practice is uncommon in India, if it occurs at all.

Origin of CJD

CJD being a very rare disease, evokes confusion with respect to what causes this disease - basically we do not know the cause of CJD (be it sporadic or variant). We may know what caused the epidemic of variant CJD, but not what caused the first case(s). Such studies, as have been done, have not associated the risk of the disease either with meat eating or in particular with eating sheep. (Studies so far have not shown an associated risk with eating meat especially that of sheep.) It has been reported that in approximately 90% of cases, CJD appears to occur randomly for no apparent reason (sporadically). About 10% of affected individuals may have a hereditary predisposition for the disorder, with suggestions that familial cases of CJD are consistent with an autosomal dominant mode of inheritance. All forms of CJD have been demonstrated to be transmissible even those which are genetically determined. If CJD occurs through a spontaneous mutation very rarely, then it is quite possible that this could occur in a vegetarian diet and not eating meat would not protect against sporadic CJD. (If CJD occurs through spontaneous mutation then it could occur in either vegetarians or non-vegetarians.)

This hypothesis overrules sheep scrapie or TSE in other species, as likely candidates. Although sheep products were incorporated into cattle feed in the UK for over 70 years, the

authors believe that the relatively late emergence of BSE belies any responsibility of scrapie as the causative agent of BSE. Moreover there is no evidence that scrapie has transmitted to man despite ongoing exposure to infectivity, unlike BSE. (Moreover unlike BSE, there is no evidence that scrapie has been transmitted to man despite ongoing exposure to infection). Furthermore the above hypothesis negates the possibility of an intrinsic origin of Bovine spongiform encephalopathy (BSE) via spontaneous gene mutations within one or more individual animals. This discrimination is based on the observed progressive rise or rise and fall of BSE cases in affected countries, suggesting an acquired cause for this disease.

Ethical manner of testing the hypothesis

The Colchesters^[1] might realize that their hypothesis creates ethical, socio-cultural, not to mention religious breaches in the scientific world. With several scientists questioning this dead tissue hypothesis, one reason for this publication is to bring to the attention of medical fraternity "how not to do science which can hurt and cause damage to social, ethical and religious matters related to a country". Given that it might not be an entirely straightforward study, efforts by the authors to screen for TSE infections or infection caused mortality around Varanasi or other banks of the Ganges, might provide some clarity around this issue. Life expectancy in India is relatively low, further reducing the likelihood of prion diseases, though this same argument could have been applied with respect to the Fore ethnic group in Papua New Guinea in which the kuru epidemic occurred. We believe that there is a parallel between kuru and the BSE epidemic, in that it was essentially

recycling of infected tissues that propagated both epidemics.

Given the fact that varied scientific reports issued over the past decade have toiled over experimental model systems to compare TSE in putative primary species with BSE in field cattle,^[3] Colchesters are unable to come up with any ethical manner of testing their hypothesis. While providing a provocative backdrop to the origin of BSE, the Colchester hypothesis while conferring immense implications (a la Pattaroyo style),^[4] leaves much to be confirmed. The Colchester hypothesis cannot be tested ethically – since such experiments would require feeding suspect human brains to cattle to screen for emergence of BSE – ‘an experiment from Hell!’ as quoted by Dr. Cashman, Canada’s leading expert on TSE or maybe ‘a page out of Frankenstein’!

The hypothesis is based on the presumption that imported animal feed way back in the 1960s was contaminated with human TSE. Yet the authors cannot prove that at that time cases of CJD were evident in India, Pakistan or Bangladesh. The authors estimate that about 120 Hindu people die from CJD every year. Yet in the last 37 years, only 85 recorded cases of sporadic CJD have been reported^[5,6] and maybe the authors might check up on the present medical standards in India before blaming “limited awareness of diagnostic features, shortage of investigatory facilities, a low autopsy rate or low reporting rate even when the disease is suspected” for these low numbers! India is a subcontinent in its own right with a population of a billion and more. Even today sporadic CJD has an unknown etiology and an incidence of around 1/million population per annum throughout the world.

To date, not a single case of BSE has been reported in India. Is this due to the cultural and religious significance of cows having a bearing on the reporting of possible cases or stressing the extremely low levels of TSE infections in this region?

The BSE epidemic

We recognize that the hypothesis that the Colchesters are putting forward relates essentially to the origin of the first case(s) of BSE and not to the subsequent propagation of the epidemic. There is little doubt that once BSE was introduced into the cattle population the propagation of the agent to cause the epidemic was due to the practice of recycling bovine tissues and feeding them back to bovines after the rendering process. Thus, the epidemic was caused by recycling the waste parts of cattle into meat and bone meal.

This is a satisfactory explanation for the spread of BSE from the UK to other countries; either because of the export of rendered material containing the BSE agent or through the export of live cattle incubating BSE. Once BSE had been introduced into other countries, epidemics were propagated in some of these because the rendering and recycling processes with respect to meat and bone meal were very similar in other countries to those in the UK. Thus, the cases, say, of BSE in Canada may have been attributable to the export of meat and bone meal to Canada from the UK and

it is not necessary to postulate any direct link between material from India and Canada.

The first cattle in the UK known to have BSE developed signs in 1984. Over the next few years the epidemic grew considerably and affected all parts of the country but to different degrees. It reached its peak in 1992, when 36,680 cases were confirmed and since then has shown a steady decline. The clinical disease usually lasts for several months and it is invariably progressive and fatal. One can question whether it is plausible that something that was introduced into the population in the late 1960s would only have produced human disease some 30 years later - on an average the time between the appearance of first symptoms and death is about 18 months. However, it is probable that the incubation period, that is the period between infection and first symptoms, is very long. Current data would suggest that, on an average, it is about 10 years.

This is similar to the average incubation period for kuru and is also similar to the incubation period for growth hormone related cases of CJD. Once BSE had been introduced into the cattle population it may have been some time before the epidemic built up to a stage that cases of BSE in cattle were recognized. It is quite possible that cases of BSE occurred in the 1970s, for example, but were not recognized as such and at least not until much larger numbers of cases occurred in the 1980s, because of the more widespread distribution of the agent, that the epidemic was actually recognized. It may be only from the late 1980s that there was substantial exposure of the human population to the agent which would be consistent with cases of vCJD occurring 10 or so years later if indeed the incubation period is generally about this long, as would be suggested by other prion diseases.

Comparison to Kuru

The authors have presented ‘substantial circumstantial evidence’ based on internet and non-substantiated book data. Years of epidemiological study have provided the cause for another TSE, namely kuru, where gender discrimination has effectively described the origin and mode of this infection.^[7] The kuru epidemic in the eastern highlands of New Guinea took the lives of 3000 individuals; more than 80% of the known kuru fatalities were recorded in a limited area populated by the fore people. Fore is a stone-age culture that, until the 1950s, practised endo-cannibalistic consumption of dead kinsmen as a rite of mourning. It was postulated that the kuru epidemic probably started with a single individual who died of sporadic CJD and was then consumed by tribesmen in the traditional ritual cannibalism fashion. Since adult men rarely ate human flesh, cannibalism was largely limited to adult women and small children of both sexes who accompanied their mothers at cannibalistic feasts. Confirming the hypothesis regarding the mode of kuru infection, it was observed that more than 75% of the described kuru victims were adult women. Children of either sex constituted the next major subgroup, the youngest case was a 4.5-year-old boy. When kuru occurred in communities neighboring the Fore region, it was observed in Fore women who had moved to marry a non-fore. These

evidence gave ample proof as to the origin of this infection (initial cannibalism of a sporadic CJD kinsman, since predominant infections occurred by this manner only). The Colchesters may need to justify their hypothesis with similar consistent epidemiological data.

Currently known TSEs include, sporadic, familial and iatrogenic CJD; Gerstmann-Sträussler-Scheinker disease (GSS); fatal familial insomnia (FFI) and variant CJD. Pathogenesis of TSE is believed to entail a conformational switch in the normal cellular prion protein (PrP-c), a predominantly α -helical molecule, into its pathogenic isoform PrP-sc that is rich in β -sheet structures, partially protease-resistant and infectious. Since prion diseases have been shown to take a number of forms in animals and humans and many prion strains that differ in their species of origin, incubation period and neuropathological targeting have been identified by passage into experimental rodents - One may well note with skepticism results of BSE strain behaviour in experimental mice strain studies. Could the complete fatality rate in response to the BSE/CJD prions indicate, besides complete susceptibility the continued passage to unnatural host species?

Future perspectives

BSE has occurred in indigenous cattle of several countries other than the UK where more strict regulations have been followed in cattle rearing and husbandry. Profile of BSE emergence in such countries point to indigenous exposure rather than acquired infection from imported cattle feed. In the US, cases of dead sheep and cow's neural tissues being mixed into the feed of cows have been reported until 1997 and the US

government said as recently as 2001 that these violations of the feeding regulation were still rampant. Cows eating the brains of other cows who already had BSE or of sheep suffering with scrapie, developed mad cow disease, providing the slogan over the media 'It is Mad to eat Meat!' a belief shared by France, Belgium and Italy.

The feeding of mammalian meat and bone meal to farm animals has been banned since 1996 in the UK and since 2001 across much of the European union. Yet sporadic cases of BSE have occurred in the UK and in Europe, where regulations have also been tightened, since the ban. A total of 309 cases were reported last year. These cases remain unexplained. Taking these arguments together it is highly improbable that the human prion disease hypothesis is valid or that the involvement of the bone trade from India is responsible for the BSE outbreak in the UK.

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