

Hypotheses on the origin and transmission of BSE

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ABSTRACT: EC Health & Consumer Protection Directorate-General recently published an important document based on papers and reviews discussed by members of TSE/BSE *ad hoc* group. In this review the Executive Summary and Tables of Contents of Part I and II are printed with permission. For full text and references see the web page mentioned in references.

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Most of information issued by European Commission, Health and Consumer Protection Directorate-General is distributed by means of an electronic bulletin CENTAUR NEWSLETTER FLASH INFORMATION – CNFI to the members of the CENTAUR network (Wojciechowski *et al.*, 2001). Reports on results of testing, opinions of the SSC and remarks to EC documents related to BSE and nCJD were the subjects of 146 and 32 issues, respectively, distributed by e-mail CNFI since March 2000 (<http://centaur.vri.cz>). “Hypothesis on the Origin and Transmission of BSE” is an important document published by EC recently (Opinion, 2001). The executive summary and table of contents are published in this review with permission as original text.¹⁾

EXECUTIVE SUMMARY

When preparing its opinions on BSE-risks, the Scientific Steering Committee (SSC) has frequently been confronted with the unknowns related to the ‘Origin of BSE’ and with ‘Alternative hypotheses for the transmission’ of this disease other than *via* animal proteins and maternal transmission. It therefore invited the TSE/BSE *ad hoc* Group to prepare two scientific reports presenting the state of affairs on both issues. At its meeting of 15 November 2001 the TSE/BSE *ad hoc* Group discussed and adopted the reports which will be updated according as new firm, data-supported evidence or soundly supported hypotheses become available.

These reports can be summarised as follows:

With regard to the origin of BSE

a) The origin of BSE remains unknown. Given the available data, the prion protein is central to TSE science and that MBM is the main vehicle for BSE trans-

mission with accidental cross-contamination of ruminant rations with MBM being an important feature in perpetuating BSE epidemics after feed bans were in place.

b) The origin of the BSE prion is also not known, and many hypotheses have been suggested, including *for example* an origin from mammalian species other than cattle (a mutant form of scrapie agent from sheep, an unmodified scrapie agent from sheep, a natural TSE in *Bovidae* or *Felidae* or other wild animals whose carcasses were rendered into MBM, the existence of a form of sporadic BSE akin to sporadic CJD of humans, a spontaneous mutation of normal bovine PrP into an infectious and protease resistant TSE prion, etc.). For none of these hypotheses is there enough data to either substantiate or to reject it. To differentiate these hypotheses the crucial issue is whether the nature of the epidemic is an extended common source or a point source followed by repeated recycling before being recognised. Regarding the origin of BSE, both hypotheses remain open.

c) Disease in an extended common source epidemic occurs more or less concurrently in multiple, widely dispersed different geographical locations that each have the same, or similar, exposure to the same contaminating infection at approximately the same time. The hypothesis of an extended common source epidemic would fit with the observations that BSE appeared in most parts of Great Britain within a short space of time, shorter than the mean incubation period of BSE and that regional differences could be explained by the epidemiological findings.

d) A point source epidemic is one originating from a singleton event, or focus, and then spreading from that point. An example would be importation of a bovine animal incubating, or affected with foot and mouth disease, but was undetected and mixed with other cattle which then became infected and dispersed the virus to other susceptible animals and species in the same or distant

¹⁾ The availability of sanco-news e-mail information to the CNFI Editor and kind permission to publish this Executive Summary is greatly acknowledged.

geographic locations. The discrimination between a point source and common source is thus not easy because a point source, at the end of the initial stages of spread, would take the characteristics of a common source. A point source epidemic is thus feasible but it would imply that in the intervening years (say 10–15 years or 2–3 incubation periods) between initial exposure and the first detected cases coming to light no veterinarian detected a new disease, nor was confident enough to submit a brain to a competent laboratory for microscopic investigation. This is considered uncertain. However, if more evidence for a point source epidemic would come forward in the future, then many currently rejected or partially rejected hypotheses (e.g. the BSE infectious agent could originate from any mammal susceptible to TSE) would become viable.

e) The report addresses the view adopted in the Horn Review dated 5 July 2001 that the unique combination of demography (large sheep population compared to cattle population and large amount of sheep waste generated for rendering), events (rendering changes) and particularly calf feeding practices in the UK is a plausible explanation of why BSE was initiated on such a scale there and not elsewhere. The Horn review also considered that there might be an age susceptibility to BSE infection and that this could be investigated experimentally.

f) It is acknowledged, however, that other alternative hypotheses on the origin of BSE exist. Some are not supported and can be rejected as not being possible to cause BSE under any condition (e.g. the autoimmune hypothesis, the bacterial (*Spiroplasma* sp.) hypothesis, the single stranded DNA hypothesis or an origin from *Coenurus cerebralis*) and others are implausible and difficult to investigate at the present time. Some of the latter hypotheses are related to the nature of the agent and how it causes its effect, such as by a toxic action (e.g. fat-associated chemical toxins in tallow or organo-phosphorous compounds) or deficiency such as an inadequate exposure to prostaglandins). If at all, they are likely to only partially and minimally contribute to the BSE epidemic, for example by altering susceptibility of an animal to TSE infection. They do not help particularly in identifying an alternative origin for BSE, but they could be important to consider once the real nature of the agent is defined and accepted. It is therefore perhaps wisest at present to still keep an open mind on the nature of the agent and to consider rather that its structure is unknown or at least uncertain.

On BSE transmission

a) There is very clear and strong support from epidemiological studies, rendering studies and the effect of feed bans in all countries with BSE, for the hypothesis of infected mammalian protein in the form of MBM being the major vehicle for BSE transmission in cattle. It can

enter the feed deliberately, or accidentally by cross-contamination. However no-one has reported so far, an experiment to test this hypothesis using compound feed with MBM containing the BSE agent rather than infected cattle tissues only.

b) The actual occurrence of cross-contamination of ruminant diets with infected mammalian protein (especially MBM), even though it is not suspected, is not considered to be a possible “third way” of BSE transmission, but part of the feed route. Cross-contamination can occur readily during feed preparation in feed mills, during transportation or on farm, unless stringent measures are taken to avoid it. Usually, cross-contamination would have been accidental. It is possible that the accidental “cross-contamination” route of exposure could account for the bulk of, if not all, assumed ‘Third Way’ cases.

c) The incorporation of infected ruminant- or mammalian-derived materials in feed other than MBM is another possibility of transmission which also is not a “third way”. Such materials might have been gelatine, fat or blood (or protein products derived from them) in which the starting materials were contaminated. Effectively enforced SRM bans and improved and authorised ruminant stunning and processing methods (including for rendering, and for gelatine and fat manufacture) should now eliminate such causes.

d) Maternal transmission is theoretically a possible route of transmission since it would appear to occur in natural scrapie in sheep. There is some statistical support for the possibility of some form of maternal transmission of BSE in cattle, but if existent it cannot account for more than 10% (c.i. 5–15%) of the offspring of all cases with BSE and probably less if transmission to calves occurs only if the dam is in the late stage of BSE incubation. However, there is no evidence so far that this so called ‘maternal transmission’ occurs in the absence of a feed borne source and no plausible mechanism for the so-called maternal transmission has been identified.²⁾ Nevertheless, it is not currently possible to eliminate maternal transmission completely as an occasional cause of BSE.

e) Any other cause than from feed or maternal transmission becomes a potential ‘Third Way’. Possible genuine ‘Third Ways’ are listed and discussed in detail in the report. Some, though unproven, may increase susceptibility to the disease. Many are theoretically possible (e.g., environmental contamination after unauthorised burial of carcasses of non-declared BSE cases) but, if existent, unlikely to have significantly contributed to the BSE epidemic. They may, however, initially have been overshadowed by the feed and maternal transmission routes of transmission and eventually become a factor in the current trend of the epidemic impeding the rapid total elimination of the disease.

²⁾ In sheep a plausible mechanism has been identified, i.e., from the placenta of infected sheep. However, comparable investigations in cattle were not conclusive.

PART I: THE ORIGIN OF BSE

TABLE OF CONTENTS

I. MANDATE AND SCOPE

II. INTRODUCTION INCLUDING SOME HISTORICAL FEATURES OF TSE ORIGIN AND TRANSMISSION

III. HYPOTHESES AND REVIEWS ON THE ORIGIN OF BSE

III.1. Original (1988–1991) hypotheses

III.2. BSE inquiry report (Inquiry 2000) on hypotheses

III.3. The horn review and hypotheses (Horn, 2001)

III.4. Autoimmune hypothesis

IV. ALTERNATIVE ORIGINS NOT DISCUSSED IN THE HORN REPORT

IV.1. Cattle origins

IV.1.1. Cattle-adapted scrapie-like agent origin

IV.1.2. 'Sporadic' BSE

IV.2. Sheep origin masked by scrapie agent

IV.3. New tse agents and dual infections

IV.4. Sporadic spontaneous conversion of PRP C TO PrP SC

IV.5. Other sources, including those that might mimic BSE, or because our current understanding of tse is later shown to be wrong

IV.5.1. The agent is a toxin

IV.5.2. The role of fat-associated chemical toxins

IV.5.3. The causes are alkaloidal glycosidase inhibitors (AGI)

IV.5.4. The agent is a bacterium

IV.5.5. The agent is a single-stranded DNA

IV.5.6. The agent is not an infectious protein but rather its structure is unknown

V. CONCLUSIONS

VI. REFERENCES

PART 2: HYPOTHESES ON BSE TRANSMISSION

TABLE OF CONTENTS

I. MANDATE AND SCOPE

II. SUMMARY OF MOST COMMONLY ACCEPTED POSSIBLE SOURCES OF BSE TRANSMISSION IN CATTLE

II.1. Feed and the oral route

II.1.1. Mammalian protein and MBM from domestic ruminants

II.1.2. Feeding of mammalian protein

II.1.3. Specified risk materials (SRM)

II.1.4. Cross contamination of ruminant diets

II.1.5. Criminal activities

II.1.6. MBM derived from captive wild ruminants and other species with TSE

II.1.7. Mammalian protein other than MBM

II.1.7.1 Gelatin

II.1.7.2 Dicalcium phosphate from bovine bones

II.1.7.3. Constituents of cattle diets that might contain gelatin

II.1.7.4. Amino acids and *Polygeline* manufactured from bovine bone gelatin.

II.1.8 Fat (tallow)

II.1.9. Tallow derivatives

II.1.10. Efficiency of the oral route

II.2. Maternal transmission

II.2.1. General

II.2.2. Infectivity studies on cattle placenta

II.2.3. Infectivity in colostrum and milk

III. THIRD WAYS OF TRANSMISSION

III.1 General concepts about 'third ways'

III.1.1. Different (parenteral) routes of delivery

III.1.2. Different infected materials as sources of infectivity

III.1.3. Genetic factors

III.1.4. Temporal changes

III.1.5. Magnitude changes

III.2. Hypotheses for other ‘third ways’

III.2.1. Environmental transmission

III.2.1.1 General

III.2.1.2. Direct horizontal transmission from cattle sources other than by placenta, milk or colostrum

- a) *Direct contact – Experimental – Mice*
- b) *Direct contact – Experimental – Sheep and goats*
- c) *Direct contact – Natural disease*

III.2.1.3 Indirect transmission from cattle or other animal sources to the alimentary tract of cattle:

- a) *Risks from soil*
- b) *Experimental studies*
- c) *Experiences in Iceland*
- d) *Risks from tissues and excretions*

Faeces

Saliva (and faeces)

Urine

- e) *Risks from plants*
- f) *Risks from fertilisers and sewage sludge*
- g) *Risks from burial*
- h) *Contaminated water*
- i) *Risks from other mammalian species susceptible to TSE or carrying infection – General*
- j) *Composted manure and stomach and intestinal contents*
- k) *Enteric nematodes (and other organisms) carrying infection*

Historical data

Blow flies and oribatid mites carrying infection

More recent studies

Hay mites carrying infection

III.2.1.4. Indirect transmission to the CNS

*Protozoon and other parasites**Coenurus cerebralis*

III.3. Iatrogenic transmission

III.3.1. Vaccines

III.3.2. Other medicinal products derived from TSE-susceptible species

III.3.3. Surgery (including use of catgut and transmission by instruments)

Blood transfusion

III.4. Genetic transmission

Genetic mutation (familial or sporadic)

III.5. Collateral factors (factors that might increase susceptibility)

- a) *The role of copper and manganese*
- b) *Exposure to organo-phosphorus (OP) compounds*
- c) *Green cluster nutrients, antioxidants and BSE*
- d) *Inadequate exposure to prostaglandins*

III.6. Other hypotheses unsupported by published articles or ‘ONE OFF’ articles

IV. CONCLUSIONS

V. REFERENCES

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