

Mad cow disease and its human equivalent — risks of infection via the Australian food chains

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Summary

Epidemiologist studies have shown that the ‘Mad Cow’ (BSE) epidemic in Britain was almost certainly caused by the practice of feeding cattle with meat and bone meal (MBM) rendered down from the carcasses of infected animals, particularly sheep and cattle. The practice created a feedback loop that magnified the transmission of BSE, creating an epidemic. It is now believed that meat or meat products from BSE-infected cattle may contain prions that can infect humans causing a fatal neuro-degenerative disease (variant Creutzfeldt–Jacob disease, vCJD). vCJD has now claimed more than 100 victims in Europe. Predictions of the eventual human toll from this disease in British residents are uncertain at this stage but may run to 250,000 and many tourists may also have been infected. BSE has now spread to European countries and almost certainly beyond, so people elsewhere in the world are therefore also at risk of becoming victims of vCJD. In hindsight, it is evident that there were numerous failings in the management of the detrimental effects of BSE on animal health and food safety in Britain. A knowledge of these failings can assist us to develop contingency plans to prevent similar events occurring in Australia.

Keywords: BSE, mad cow, CJD, rendering, meat meal, prion

Introduction

Globally, each year 68 million metric tonnes (Mt) of pure protein are provided in feed prepared for farm animals, mainly pigs and poultry, that become meat for human consumption. Of the protein used, 86% is from plants, mainly soybean, and the remaining 14% is made up of animal proteins from by-products of meat production (5.5 Mt produced mainly in North America, Europe and Australia) and 3.9 Mt from fish that are caught and not used for human consumption (WHO 1999). The rendering industry plays an important role in the recycling of animal proteins (and fats) that has been implicated in the ‘Mad Cow’ epidemics (Bovine

Spongiform Encephalopathy, BSE) in Europe. The practice of feeding rendered down ruminant offal from infected animals in the form of meat and bone meal (MBM) back to animals of the same species was central to the development of the BSE epidemic in Europe with its subsequent tragic human consequences.

The unfolding of the ‘Mad Cow’ disease saga in Britain has many other fascinating twists and we in Australia have much to learn from our counterparts in the UK and Europe. The story exposes wider issues relating to how scientists interacted with politicians and other policy makers, and how all ‘experts’ interacted with the public at large. Overseas the epidemic will continue to involve farmers, scientists, medical and veterinary professions and consumers—in fact all members of the public. In Australia, there are lessons to be learnt from the epidemic in relation to feed processing, cattle disease surveillance, medical implications and other matters.

TSEs

There is a family of neuro-degenerative diseases of humans and other mammals, similar to BSE, that cause irreversible brain damage and are invariably fatal, the Transmissible Spongiform Encephalopathies or TSEs. At autopsy the brain has a characteristic sponge-like appearance.

The sheep disease, scrapie, is a TSE. The disease has been recognized for nearly 200 years but does not appear to be easily transferred to humans or other animals. In humans, Creutzfeldt–Jacob disease (CJD) was described in the 1920s by the workers after which the disease is named. It is a dementia that appears sporadically in people in all countries, affecting one person in a million, typically at about age 60. There are about 20 deaths each year in Australia from this so-called ‘sporadic–CJD’.

In 1957, the disease kuru in the Fore Highlanders in Papua New Guinea was found, by Vincent Zigas of the Australian Public Health Service and D. Carleton

Gajdusk of the U.S. National Institutes of Health, to be a similar spongiform encephalopathy. These workers found this disease, now known to be a human TSE, was spread between the highland people by a form of ritual cannibalism in which they honoured their dead relatives by eating their brains. Incidence of the disease has declined rapidly since cannibalism ceased in 1959, but clinical cases of the disease have continued to appear, the latest in September 2000. Long 'incubation' periods (measured in years or decades) are characteristic of all TSEs that, until the 1980s, were thought to be caused by so-called 'slow viruses' (e.g. Gajdusek 1977).

Bovine Spongiform Encephalopathy is another TSE that was only discovered in 1986 in cattle in Britain. The infective agent, generally accepted to be a 'proteinaceous infective particle' or 'prion' for short, is thought to be spread mainly by animals ingesting protein meals made using rendered down offal from infected animals (cf. cannibalism and kuru), and to a minor extent by transmission from cow to calf. BSE has an ability to jump the 'species barrier' and to cause neuro-degenerative disease in humans and other mammals. In humans, a new variant of CJD was diagnosed in a young man who died in 1995. It is referred to as variant CJD (vCJD) to distinguish it from the long-recognised sporadic CJD. The factors that contributed to amplification of BSE and its putative transmission to humans are shown in Figure 1.

'Mad Cow' disease

When BSE or 'Mad Cow disease' was first acknowledged by the British Ministry of Agriculture, Food and Fisheries (MAFF) in 1986 (see Figure 1), there was probably little reason for most scientists to suspect it might cross the species barrier and affect humans. (Scrapie had been recognized in sheep for 200 years, and was thought never to have infected humans.) However, it was recognized by Dr. John Wildesmith, Head of the Central Veterinary Research Laboratory at Weybridge, that BSE might be spreading within cattle herds via the practice of feeding MBM made from BSE-contaminated carcass remnants from slaughtered animals. Retrospective analyses by Donnelly *et al.* (1997a) later suggested that BSE had been spreading via MBM in Britain well before 1986 and that a BSE epidemic in British cattle was already developing in the early 1980s. It would have been assisted by widespread MBM feeding, especially to dairy cattle. Subsequent computer models suggest that, without MBM in cattle feed, the epidemiological reproduction number (see Deikmann and Heesterbeek 2000) would have been less than one, and a BSE epidemic would not have developed (de Koeijer *et al.* 1998).

In 1988, the British government outlawed the practice of feeding MBM made from ruminant offal to cattle, thereby in theory removing the principal reason for the multiplication of BSE among cattle. At that time

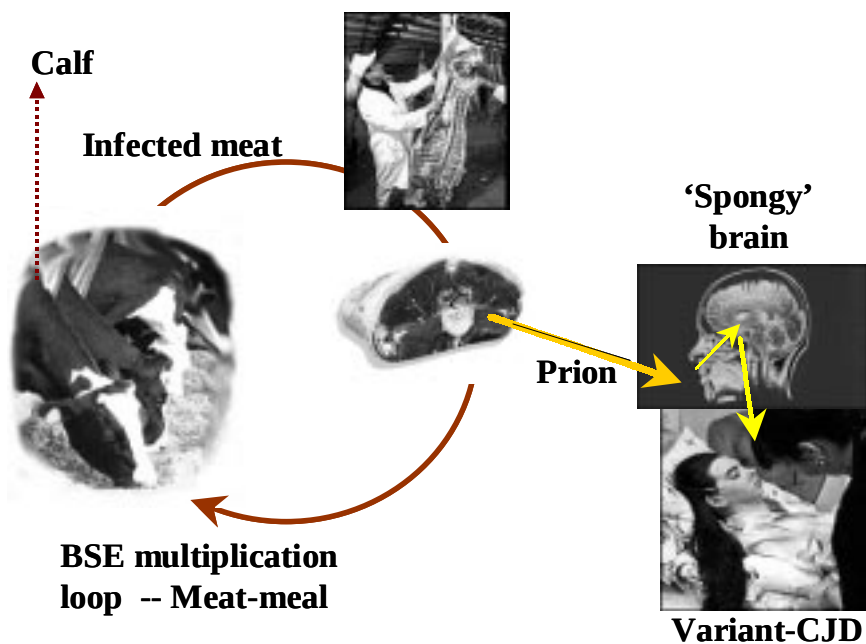


Figure 1 Factors enabling multiplication of BSE, the transmission of BSE to humans by ingestion of BSE-infected meat, and the development after an 'incubation period' of perhaps decades of clinical signs of vCJD.

there were 41 rendering plants producing 0.35 Mt MBM and 0.23 Mt tallow (Southwood 1989). However, ignorant of the fact that the rate of infection at that time was thousands of cases a week, the government allowed a 'period of grace' of 5 weeks for renderers to clear existing stocks. In addition, because BSE-infected cattle silently harbour the infective agent for many years before clinical signs become evident, and because the feed ban was flouted or misunderstood and cross-contamination between ruminant and non-ruminant feeds continued in feed mills, the numbers of new diagnoses of BSE continued increasing until 1993, a year in which there were nearly 40,000 confirmed cases. There have now been about 178,000 officially confirmed cases of BSE in Britain, and new cases are still appearing in 2001. All BSE confirmations have been made by post-mortem examination of brain tissue: there are still no totally reliable tests for BSE in living animals.

Back calculations suggest that at least 1 million cattle (six times the number of confirmed cases) have probably been infected with BSE to date (Figure 2). Many of these cattle were slaughtered to provide meat, and thus many thousands of British people and many tourists would have eaten BSE-infected beef during the height of this epidemic. These people may still be silently 'incubating' BSE infections (perhaps acquired up to 20 years ago) and may in the future develop vCJD. Fortunately, a ban preventing the inclusion of brain and

nervous system (thought to be highly infective tissues) in meat products destined for human consumption was imposed in 1989. This ban probably reduced the risk of human infection but would not have eliminated it. Moreover, quality assurance procedures were not in place and the ban was not universally observed. Since 1993, the cattle-BSE epidemic has been subsiding. This year only about 30 new BSE cases per week are being diagnosed by post-mortem brain testing in Britain, and authorities expect that BSE incidence will continue to decline over the next few years.

From the time BSE was first recognized, warnings were made of the potential threat of transmission of the BSE agent to humans (e.g. Holt and Phillips 1988). Subsequently, in the years when the BSE epidemic was prominent (1990–1995), British politicians and public officials, to allay public concerns, claimed on many occasions that 'British beef is safe to eat'. Minister for Agriculture, Gummer's assertion to this effect has become one of the most celebrated examples after he posed for the media in 1990 with his four-year old daughter Cordelia, as both ate hamburgers to demonstrate the safety of British beef! However, many other public officials, including the Chief Medical and Veterinary Officers and later the Secretary of State and the Prime Minister, made similarly soothing statements, and we know now how misplaced those public assurances were.



Figure 2 The numbers of cattle putatively infected with BSE in Britain between 1982 and 2001 (after Donnelly *et al.* 1997a with addition of MAFF data after 1996) and the timing of some significant events relating to the history of BSE.

Spread of BSE to other countries

The BSE trail now extends beyond Britain and probably world-wide. Unfortunately, although feeding of MBM to ruminants was no longer permitted in Britain, after 1998 large tonnages of meal were still exported. MBM was exported to more than 70 countries (the risk of, and consequences of, BSE transfer overseas being considered to rest with the recipient country). Recipients of the meals made from offal from potentially infected British cattle included European countries, Japan, Thailand and Indonesia (*Sunday Times*, London, 4 February 2001). In March 1996 the European Commission (EC) introduced a ban on the export from the UK of bovine animals, semen and embryos, beef or beef products and mammalian MBM but, unfortunately, total bans on exports of meals from other EC countries were not implemented until January 2000.

In response to the 1996 export ban, a concerned British Government implemented two control programs: culling of animals over 30 months of age (OTMS), and a selective cull of herds with a history of high incidence of BSE. About 1.4 million cattle were slaughtered under the OTMS in 1996–97, and 19,271 cattle were selectively culled. However, the records of these culling programs were deficient. Donnelly and co-workers have attempted to study the impact of both programs, but found this was difficult because records were not kept on the ages of animals slaughtered under OTMS and there was limited information on the animals selectively culled from high-risk herds.

Between 1988 and 1996, while the BSE epidemic was at its highest, Britain exported 3.2 million 'BSE-free' cattle to 36 countries throughout the world. EC countries also exported millions of cattle worldwide. In contrast to the declining BSE incidence in Britain, in some other EC countries, numbers of confirmed BSE cases are increasing (Figure 2; CompuServe, 2001).

Donnelly's modelling group (Donnelly 2000) has estimated that, since 1987, at least 1200 French cattle have been infected by BSE-infected cattle from Britain and similar infections have probably occurred in many other countries. Some countries in Europe have only recently discovered BSE in their cattle: in the future others such Romania and the Czech Republic will almost certainly find they have the disease. BSE has been detected in Canada, Oman and the Falkland Islands in cattle imported from Europe. It is likely that BSE is now present but undetected in other parts of the world.

Outside Britain, another BSE epidemic is probably looming and it may therefore be many more years before BSE is brought under control globally.

The BSE infective agent — the prion

Most infections of animals and people are caused by bacteria or viruses that replicate and thereby spread disease. The infective agent of TSEs is now thought,

by most scientists, to contain no nucleic acid and to be a relatively small proteinaceous particle or 'prion'—a name coined by Dr Stanley Prusiner and co-workers (see Prusiner 1982). Prusiner was awarded a Nobel prize in 1997 for his contribution to an understanding of the role of prions. In the early 1980s, to suggest as Prusiner did, that a protein particle alone could be infectious was a scientific heresy. It was thought that no organism on the planet could replicate without the participation of nucleic acid. It is perhaps for this reason that a minority of experts still believe that the prion may not act alone in causing TSEs.

It is fascinating to note that the now widely accepted theory of how protein particles could replicate and be infective had been described in 1967 by a mathematician (Griffith 1967) and quickly dismissed. Griffith argued that the same genetically determined protein particle would have to be able to exist in two different forms in cells—in its normal cellular structure (healthy cells), or in another disease causing conformation. It is now thought that a naturally occurring glycoprotein molecule that is rich in alpha-helical regions switches to a thermodynamically more stable beta-rich isoform (Baskakov 2001) that is highly insoluble and protease resistant (Horwich and Weissman 1997). All higher animals have a highly conserved gene that controls the formation of a 35 kD protein that is found in the membranes and contents of normal nerve and immune system cells. The normal protein is synthesized in three topologic forms at the endoplasmic reticulum (ER) (Hegde *et al.* 1999). The predominant isoform is fully translocated into the ER lumen, while the other two forms are single-spanning membrane proteins. A similar form occurs in all mammals and is thought to play a role in the metabolism of nucleic acids (Gabus *et al.* 2001) and copper at synapses (Kretzschmar *et al.* 2000). Copper alters the biochemical properties of this protein by directly binding to its N-terminal region and may play a role in its conversion to a protease-resistant isoform (Quaglio *et al.* 2001). Prion protein (PrP) appears to be necessary for normal synaptic function: nevertheless, mice homozygous for disrupted PrP genes appear developmentally and behaviourally normal (Collinge *et al.* (1994).

In animals developing TSEs the normal *cellular* protein forms may suddenly flip from their normal structure into the *protease-resistant* disease provoking form, especially if triggered by the presence of a closely related abnormal protein (prion) acquired from another animal via infected food, or perhaps via contaminated surgical instruments, blood or donated tissues. A chain reaction ensues with formation of large amounts of the protease-resistant protein molecules that are associated with the death of nerve cells and the spongiform appearance of the brain at autopsy.

Prions that are ingested in MBM by farm animals or in meat or meat products by humans may be absorbed across the gut wall at Peyer's patches that are part of the mucosa-associated lymphoid tissue (MALT).

Lymphoid cells may engulf the particle by phagocytosis and then travel to other lymphoid tissues such as lymph nodes, and the spleen and tonsils where the prion can probably promote the change in confirmation of its normal cellular analogues. Mature B lymphocytes are apparently necessary for disease to establish following infection of animals via a peripheral route (Weissmann *et al.* 2001). After an extended silent period, cattle develop BSE and humans develop vCJD.

The infectivity of prions after rendering

Prions are not only protease-resistant, but also highly resistant to most treatments used to eliminate pathogenic viruses and bacteria: autoclaving, hospital detergents, alcohol, UV radiation, gamma irradiation, microwave radiation, hydrogen peroxide, chlorine dioxide. They are therefore particularly difficult to eliminate from the environment.

BSE-infected material was found to be still infective after being buried for 3 years and, which almost defies belief, hamster-adapted scrapie agent (263K) survived combustion at 600°C for 15 min (Brown *et al.* 2000). In short, prions in the environment may remain infective for a very long time! They are also resistant to natural digestive enzymes and to intracellular proteases, including those that remove their normal counterparts in healthy cells. In the infected animal cell, the prion form is associated with build-up of white plaques in brain tissue and somehow promotes death of brain cells, leaving the sponge-like brain appearance that is characteristic of vCJD. It has been claimed that an infected piece of tissue 'the size of a peppercorn' is sufficient to infect a cow and it has further been suggested, but not scientifically verified, that one infected cow could potentially infect hundreds of thousands of people.

Taylor *et al.* (1995) used bovine brain samples infected with the BSE agent to spike materials (representing those rendered in commercial plants). The spiked material that was then processed into MBM and tallow in pilot scale facsimiles of 12 rendering processes then being used within the European Union, and three others. Suspensions of all the MBM samples and two of the tallow fractions were assayed in inbred mice for BSE infectivity. MBM from four of the 15 processes showed detectable BSE infectivity whereas the tallow samples had no detectable infectivity. Taylor (1996) found that the infectivity in macerates of mouse-brain infected with the ME7 strain of scrapie agent was not completely inactivated by exposure to dry heat at temperatures up to 180°C for 1 h but infectivity was reduced progressively as the temperature was increased. No infectivity was recovered after a 1 h exposure at 200°C. The resistance of the prion to destruction means that the minimum conditions normally used to render beef offal in Australia (120°C at 2 bar for 20 min) certainly could not be relied upon to remove BSE infectivity.

Because the rendering conditions do not completely remove prion infectivity, huge quantities of potentially infective offal are still being produced in Europe and the question is: how can the MBM being fed to pigs, poultry and fish be processed to guarantee that it no longer poses a risk of infecting animals or people in the food chain? In Europe, since 1996 all EC rendering plants producing mammalian proteins destined for farm-animal feeds are capable of meeting pressure-cooking standards (133°C at 3 bar for 20 min). There is, however, currently a ban in the EC on feeding the resulting meals to farm animals. This ban may be lifted in the future when current failings in the processing and distribution of MBM have been overcome. For the EC to lift the ban, certain principles would need to be guaranteed:

- only animal by-products considered fit for human consumption should be rendered down to MBM
- there should be a complete separation of animal feed from wastes not fit for human consumption
- plants dedicated to animal feed production should be separate from those processing other animal waste.

Until the present, cross-contamination between general animal and ruminant feeds in feed mills has been found to be widespread in many EC member states (EC 2001).

Meanwhile, there are plans to incinerate 3 Mt of MBM unfit for use for animals that have been stockpiled, along with partially rendered carcasses that have been stored in various locations. (In the EC, 14 Mt of MBM are produced annually.) However, incineration is not feasible in the short term because there are not enough suitable incinerators, and other methods of benign disposal are urgently needed.

In this connection it is pleasing to note that an Australian company, Australian Dehydration Technologies Pty Ltd (ADT), managed by a graduate of the UNE, Mr. Phil Kemp, has patented a new process for rendering meat products. This is a biochemical process (alkaline hydrolysis) that is claimed to be more energy-efficient than conventional rendering and uses simple and inexpensive technology. The MBM produced is of high quality and has excellent keeping properties.

At UNE, we have evaluated MBM made from kangaroo offal by the ADT process against conventional MBM in diets used to grow female broiler chickens from 5 and 20 days of age. MBM was included at a level of 12% in a standard formulation consisting of sorghum (48%), wheat (20%), soybean meal (20%) and 0.35% of both DL-methionine and L-lysine. The mean values for feed intake and growth rate per bird and feed conversion efficiency did not differ between diets and were 54.5 g/d, 38.2 g/d and 1.4 g/g respectively. The results indicate that the ADT-rendered MBM from kangaroo offal can replace conventional MBM without affecting chicken growth.

Ironically, the alkali-rendering technology might turn out to be an ideal way of removing BSE infectivity in animal carcasses. The alkali is likely to be able to chemically alter the prion, thereby removing its functionality and its ability to infect animals or people. Support for this concept is given by work of Ernst and Race (1993) who demonstrated that, when scrapie-infected hamster brain homogenates prions were treated with 0.1M sodium hydroxide for 2 h, followed by autoclaving at 120°C for 1 h, prions were inactivated. Taylor *et al.* (1999) found that there was no infectivity in samples spiked with the highly thermostable 301V strain of mouse-passaged BSE agent after boiling samples containing the agent in 1M sodium hydroxide for 1 min. The patented ADT rendering process is currently under investigation in Scotland to determine if it also eliminates the infectivity of meat products spiked with thermo-stable TSE agents (P. Kemp, pers. comm.).

Where did BSE come from?

The source of BSE is still unclear. In her comprehensively researched book, Cooke (1998) has summarized the various theories on the origins of BSE, often assisted by personal interviews with relevant people. One suggestion is that scrapie-infected sheep were rendered into MBM and the sheep-cattle species barrier was breached by changes in rendering conditions. The removal of solvent extraction and introduction of lower temperature 'continuous flow' cooking in the late 1970s and early 80s may have increased the likelihood of this chance occurrence. An adjunct to this theory was the suggestion that a mutant strain of scrapie had jumped the species barrier. However, Dr. Alan Dickinson, Head of the Neuropathology Unit in Edinburgh (a scrapie expert interviewed by Cooke) has argued that it is unlikely that scrapie would have crossed a species barrier that had existed between sheep and cattle for more than a century. He suggested that the BSE agent might have been imported in a cow from another country. Recently, Professor Morris, Massey University has added a further possibility (AP 2001), that an African antelope brought the TSE into safari parks in southern Britain and BSE developed from there. Ford (1995) on the other hand suggested that BSE has long existed in Britain as a 'sporadic' TSE specific to cattle. The feeding of MBM manufactured from cattle offal under less rigorous conditions simply amplified a 'sporadic' cattle TSE.

An associated theory for the origin of BSE has been promoted by UK farmer, Mark Purdey. He suggests that instability of the normal conformation of the normal cellular protein resembling the infective agent (a metallo-protein) may arise when the diet of the animal contains unusually high ratios of manganese relative to copper, leading to a greater likelihood that prions will be formed and the animal will develop a TSE. He claims

that clusters of prion-related diseases have occurred in regions with high levels of manganese in conjunction with low levels of copper. These clusters could also be related to the practice of feeding mineral supplements to cattle (Purdey 2000). His theory does not, however, explain why BSE has appeared only in British cattle if genuinely similar conditions have existed elsewhere.

Human BSE — a global epidemic?

Since the first case of a new variant of Creutzfeldt-Jacob disease (vCJD) was confirmed as the cause of death of a young man named Steven Churchill in Britain in 1995, there has been overwhelming, albeit circumstantial, evidence linking the fatal human disease to the incidence of BSE. Humans who develop this disease lose motor function, suffer memory loss and hallucinations, progressive brain damage, and eventually die. In contrast to the long-recognised 'sporadic CJD' which usually occurs in older people, vCJD seems to infect younger people. Recent reports have confirmed that vCJD is distinct from sporadic and acquired CJD (Ironsides 2000). vCJD has affected younger patients (average age 29 years, as opposed to 65 years), has a relatively longer duration of illness (median of 14 months as opposed to 4.5 months) and is strongly linked to exposure, probably through meat or meat products, to BSE (WHO 1999). The reasons why vCJD affects mainly younger people are not clear, although some experts argue that young people are more likely to eat reprocessed meat – this meat being more likely to contain neural and lymphoid tissues (SBOs) that are considered to be more infective than other beef products.

At the time of writing, 103 people have died of vCJD. They probably acquired the infection 10–20 years before their death (the putative 'silent' period before vCJD symptoms appear), i.e. in the 1980s. Notably, all the deaths so far have been in people with a genetic condition that occurs in about 30–40% of the population, i.e. homozygous for methionine at codon 129 in the prion-protein (PrP) gene. Codon 129 can also code for valine but there is no evidence that vCJD has occurred in Britons who are MV or VV at codon 129 in the PrP gene (Ironsides 2000). This could mean either that these people are not susceptible to vCJD or, because polymorphisms in the prion gene are known to affect incubation times and TSE susceptibility in humans and mice (Collinge *et al.* 1991; Westaway *et al.* 1987), that BSE incubation periods in these latter groups may be longer than in methionine homozygotes. It is therefore almost impossible at present to predict the likely numbers of future cases of vCJD in Britain. The scenario, however, is clearly a grim one; the question is 'how grim'? Workers at Oxford University (Ghani *et al.* 1998) have used models based on conservative assumptions (e.g. that the disease affects only genetically susceptible people in younger age groups) to predict the likely future deaths from vCJD in Britain and their

estimates range from 20,000 to 136,000. A new set of predictions due for release shortly, is likely to suggest the deaths for vCJD could exceed 250,000.

To date only a few confirmed cases of vCJD have occurred outside the UK. In European countries and elsewhere, the situation is even less clear than in Britain, but it is possible that many countries may unknowingly have imported infected cattle or infected MBM or meat products and may already have BSE infection in both cattle and human food chains.

Against this background, the World Health Organisation (WHO 2000) has recently stated:

the future potential public health threat of vCJD— not only in the UK but in Europe and the rest of the world—is alarming, and currently unquantifiable.

Phillips Report

An official inquiry into events leading to the human disease consequences of the BSE epidemic was set up at the end of 1997 by the Blair Government 'to establish and review the history of the emergence and identification of BSE and new variant CJD in the United Kingdom, and of the action taken in response to it up to 20 March 1996; to reach conclusions on the adequacy of that response, taking into account the state of knowledge at the time; and to report on these matters to the Minister of Agriculture, Fisheries and Food, the Secretary of State for Health and the Secretaries of State for Scotland, Wales and Northern Ireland' (Phillips 2000).

In the first phase of the BSE inquiry in 1998 evidence was taken from more than 300 witnesses and more than 400 written statements were published. In Phase two, which took place in 1999 and 2000, witnesses were recalled and the evidence more closely investigated. Giving evidence was Roger Tomkins whose daughter, Clare, a vegetarian since 1986, had advanced vCJD. If Clare had indeed not eaten meat during her years as a vegetarian, it could indicate that she was infected by beef products in, for example, cosmetics or that the infection occurred some time before 1986 and the clinical signs of vCJD took more than 10 years to appear. This case turned the spotlight on the early period of the BSE epidemic and, in this connection, Donnelly *et al.* (1997a) estimated that, depending on their assumptions about under-reporting, up to 54,000 infected animals were slaughtered for human consumption before clinical onset of BSE between 1980 and 1985. Over the whole period of the epidemic, more than 1 million BSE-infected cattle may have entered the human food chain (Raymond *et al.* 1997).

Politicians, public officials and members of the public gave evidence. Sir Kenneth Calman who as Chief Medical Officer had reassured the public in

1993 that beef was safe to eat, explained to the inquiry that his earlier reassurances that beef was safe to eat 'did not mean there was no risk'. His comments, taken at face value, highlight how differently statements and assurances may be interpreted by members of the lay public.

At the end of the BSE hearings in 1999, Lord Phillips, the Committee's chairman, said: 'It is now for us to prepare a report which identifies what went right and what went wrong and draws attention to the lessons to be learned for the future.' The inquiry presented its report to the government in October 2000 (Phillips 2000). At that time, the BBC website provided the following summary of the Committee's main findings.

BSE developed into an epidemic as a result of an intensive farming practice—the recycling of animal protein in ruminant feed. This proved a 'recipe for disaster'.

Government ministers played down the links between BSE-infected beef and variant Creutzfeldt–Jakob Disease. They also misled the public about [the extent of] the risks posed by mad cow disease.

Up to March 1996, most of those responsible for responding to BSE did so with credit, though there were shortcomings.

The government was too preoccupied with preventing a panic reaction to BSE and therefore the way in which the risk was communicated to the public was flawed.

Although a ban existed in 1989 to prevent specified bovine offal—brain, spinal cord and other tissue—entering the human food chain, there was a failure to enforce it properly.

A failure to ensure proper communication between government departments meant the Department of Health was not kept informed of the increasing weight of evidence proving a link between BSE and vCJD.

Ministers and civil servants failed to develop any contingency plans to cope with a situation where vCJD was found to be caused by BSE-infected beef despite the fact that years had passed since the first evidence of a link had been uncovered.

The government relied too much on experts from the spongiform encephalopathy advisory committee (SEAC) to formulate policy and spent too long consulting with experts before implementing advice.

A 'lack of rigour' was applied when considering how to turn policy into practice, partly because until early 1996 many believed there was no threat to human life. The Ministry of Agriculture did not favour agriculture producers over consumers.

The Meat and Livestock Commission is accused of 'absurd exaggerations'.

The Commission's 1995 advertising campaign that aimed to reassure people about the safety of beef created a climate where 'hyperbole replaced accuracy'.

A combination of delays and denials prompted the public to feel deceived and undermined their confidence in public statements.

The probable link between BSE and vCJD was identified as early as reasonably possible. The link is now clearly established, though the manner of infection is not clear.

A recent response to this Inquiry by an Australian committee (AFFA–BSE 2001) noted that the absence in Britain of an appropriate model for risk analysis was a major detriment to the management of the BSE crisis. The task force argued that appropriate risk analysis and risk assessment could have helped authorities in Britain in several ways, viz. to evaluate the probability of adverse human health risks from contaminated meat, to weigh policy alternatives, and to exchange information between scientists, risk assessors and policy makers in a meaningful way. Accordingly, the task force recommends that 'a program be developed in Australia to raise awareness of the nature of risk analysis in industry, government and the scientific support services.'

The future in Britain

The aftermath of the BSE–vCJD epidemic in the UK is far from over.

A study of cow–calf BSE case data by Donnelly *et al.* (1997b) revealed a maternal transmission rate from cows to calves beginning up to 2 years before the clinical signs of BSE in the cow, rising to about 10% in the last 5 months of the disease. This vertical transmission route can be expected to generate new cases of BSE for some years to come, but may not be sufficient to sustain BSE in the long term.

This year (2001) there are still about 30 new cases being confirmed each week. The new cases are mainly in older animals. Some cases may also be a result of vertical transmission from cow to calf, or because a low level of contamination of cattle feeds with infected meat or meat products is still occurring. Since the OTMS scheme was introduced, potentially contaminated 'specified bovine offals' have been stored in large amounts in unused warehouses and aircraft hangers whilst awaiting incineration (Barnett 1999). The transport and handling of this material may have created a potential for low–level contamination of cattle. Similarly, on–farm feed storage areas or feeding troughs could have retained some infectivity and allowed carry–over of the infected agent into more recently acquired feedstuffs.

Late last year, Professor John Collinge and co–workers at the Prion Research Unit in London declared that sheep, pigs and poultry products could theoretically pass BSE on to humans (see Collinge 2001). Transmission of BSE to sheep, which can apparently carry BSE without showing symptoms, is a possible secondary route of transmission of BSE to humans. If such a route exists, in Europe (but fortunately not in Australia), mutton could already have been a secondary source of transfer of BSE to humans.

The future in other EC countries

More European countries have recently confirmed they have BSE in their cattle (Figure 2) and accordingly the EC has, since January 2001, required mandatory testing in its member countries of all 'at risk' cattle (the latter to include fallen stock and emergency or causality–slaughtered animals) and will, after July 2001, require testing of all cattle over 30 months of age (OTMS) destined for human consumption. The EC countries have placed a ban on the use of feed containing MBM for all animals, and on the sale of meat taken from near the spinal cord.

Scientific advisors believe other non–member eastern European countries are likely to have BSE in their herds. 'High risk' countries classified in May 2001 as 'Category III', i.e. likely to present a BSE risk, were Albania, Cyprus, Czech Republic, Estonia, Hungary, Lithuania, Poland, Romania, Slovak Republic and Switzerland. All countries not classified as Category I ('unlikely to present a BSE risk') are required to remove spinal cord and other potentially infective tissues from meat at the slaughterhouse if they intend to export it to the EU.

BSE in Australia

Fortunately, for people in Australia, all available information indicates that there is no BSE in Australian cattle (or other TSEs in other farm or feral animals) and the likelihood of our cattle acquiring infection is very low. We should not therefore be at risk of acquiring vCJD as a consequence of eating Australian grown meat or meat products. Three key measures should ensure Australia remains BSE free:

- strict controls and restrictions on imports of live animals, semen and ova, and animal feedstuffs
- a ban on feeding MBM to ruminant animals, and
- a national surveillance program (AFFA–APH 2001).

These measures are also important in maintaining market access with trading partners, and to reassure domestic and overseas consumers of the safety of Australian beef.

Australia is one of 11 countries currently judged to meet 'Category 1' status—the lowest BSE risk. Our quarantine and surveillance measures meet or exceed OIE (Office International des Epizooties) and WHO recommendations. However, we might still ask: *are these standards sufficient? Will these standards alone enable Australia to maintain its perceived TSE-free and favoured trading status?*

Klim (2000) reports that Australian agricultural and human health officials have been reviewing the potential for downstream effects if BSE entered Australia in the context of a wider monitoring of TSEs. AFFA (Agriculture Fisheries and Forestry Australia) has been monitoring TSE issues in Australia. Under the auspices of AFFA are Product Integrity and Animal Plant Health, the Australian Quarantine and Inspection Service (AQIS) and Biosecurity Australia, as well as the Department of Health and Aged Care (DHAC, which includes the Therapeutic Goods Administration and the Australia New Zealand Food Authority, ANZFA). AFFA have studied the Phillips Report and begun a risk assessment in relation to importation of foods from BSE-affected countries (AFFA-BSE 2001).

The Australian National Health and Medical Research Council (NHMRC) has established an Advisory Committee on TSEs (Special Expert Committee on TSEs, SECTSE) under the Chairmanship of Professor Graeme Ryan (pathologist and medical academic) with 15 other members, two of whom are veterinarians—Drs. Chris Baldock and Kevin Doyle. "The committee will study the full range of TSEs, including BSE in cattle, scrapie in sheep, 'classical' Creutzfeldt-Jakob disease (CJD) and variant CJD in humans, and advise the Government on how best to deal with these emerging issues based on sound evidence and best practice" (McNiece 2001). Importation of stock feeds with animal components (including MBM) into Australia has been prohibited since 1966. Use of locally produced MBM in ruminant diets was banned voluntarily in 1996 and enforced by legislation in all States and Territories in 1997. The ban was extended to include the feeding of specified mammalian protein materials to ruminants in 1999 (Klim 2000). Compliance with these bans is said to have been 'evaluated by periodic audits of renderers and feed manufacturers' (AFFA-APH 2001). However, it is not clear how frequent, extensive or effective these audits have been.

At its meeting in Wellington in March 2001, the Agriculture and Resource Management Council of Australia and New Zealand (ARMCANZ) agreed to implement a national approach to BSE prevention through tighter surveillance and monitoring systems. This Council consists of the Australian Federal, State/Territory and New Zealand Ministers responsible for agriculture, soil, water and rural adjustment policy. ARMCANZ acknowledged it was essential that Australia learnt from overseas experience and built on its previous control measures 'through the development, effective resourcing, implementation and uniform

enforcement of a comprehensive risk management strategy'. ARMCANZ agreed to:

- establish a National Management Group to advise SCARM/ARMCANZ and work closely with health authorities, NHMRC and industry
- introduce legislation in States and Territories to strengthen and extend the existing ban on certain classes of feedstuff to ruminants and to audit compliance with those feed bans, and
- ensure a number of activities are supported and progressed including surveillance, imported cattle identification and quarantine.

These and other issues require continuing review. What, for example is meant by 'strengthen and extend existing feed bans', and is this 'extension' justified scientifically? How well, scientifically, are the ARMCANZ State and Territory Ministers advised? **Some other issues requiring on-going review by these advisers, and by all policy makers are made in bold type below.**

In Australia, the feeding of ruminant-derived MBM to ruminants is banned but is still allowed for pigs and chickens. New research findings concerning whether TSEs can cross the 'species barrier' and be carried 'silently' by non-ruminant animals that eventually enter the animal or human food chains could affect this situation. It would seem sensible to call for an **on-going review of whether the feeding of animal protein to non-ruminant livestock** (pigs, chickens and perhaps fish) **should be banned**. Such a review has also been recommended by AFFA (2001) who, in addition, point out that compliance with bans needs to be monitored by quality assurance and audit procedures.

In response to the outbreak of BSE in Britain, we have had quarantine regulations in place since 1988 preventing the importation of live cattle (about 500 cattle imported from the UK and Ireland in the 1980s have been traced). The restrictions on live cattle imports have been extended to include France and Switzerland following the confirmation of BSE in those countries. Nevertheless, as suggested above, we should assume, in the absence of sound evidence to the contrary, that other countries, including those in Asia, have BSE in their cattle. Accordingly,

- **the importation of live cattle and beef and beef products from all 'at-risk' countries, including all those countries that have not been effectively assessed, should be banned immediately**
- **the decision to relax restrictions on importation of embryos and semen from cattle and sheep should be subject to on-going risk assessment by SECTSE**
- **a database of recently imported cattle, cattle**

embryos and semen with information capable of enabling tracing of cattle in the future should be established immediately.

On-going surveillance of cattle in Australia by the National Transmissible Spongiform Encephalopathies Surveillance Program commenced in 1990. The program, jointly funded by industry and governments, aims 'to demonstrate Australia's on-going freedom from BSE and scrapie and to provide early detection of those diseases should they occur'. The TSE surveillance system was enhanced in 1998 to meet the OIE International Health Code (May 1998 revision) that specifies the number of eligible cattle and cases requiring examination across Australia each year (Table 1). The task of collecting samples is divided between State authorities and AQIS meat inspection. For brain tissue to be eligible for examination, cattle must meet certain neurological criteria related to mental status, sensation, and posture and movement.

Of concern is that current tests, and those under evaluation, can potentially detect only animals with clinical signs of BSE. However, if infection occurred asymptotically in cattle in Australia, the disease might exist undetected and be disseminated (by cow calf transmission or carcass eating for example) for 5–6 years. **Scientific research should be undertaken to find ways of detecting BSE infection in its pre-clinical stages and, if the potential risk is deemed sufficient to warrant it, random sampling and testing of the general cattle population should be implemented.**

In addition to current testing, the Australian Animal Health Laboratory (AAHL) has been working to improve its BSE testing capabilities. A veterinary committee has been considering the introduction of a rapid post-mortem test (immunology based) for detecting BSE using one of three tests endorsed by the EC's Scientific Steering Committee and these tests are being evaluated at AAHL (Klim 2000). Dr. Deborah Middleton from AAHL has recently completed a study

tour in Europe where she visited institutions concerned with BSE diagnostic tests. Additionally, AFFA (2001) has recommended **that scientific research should be promoted to obtain a better understanding of BSE in the context of other nervous disorders of livestock that could be mistaken for BSE.**

Quarantine and food importation

Importation of suspect meat and meat-containing food products from more than 30 countries has been subject to a progressive (temporary) 'suspension' since January 2001, thereby extending a prohibition on import of certain beef products first imposed in 1996. DHAC initiated the suspension by asking the grocery industry ... to introduce a *voluntary* withdrawal of relevant products and advised consumers to dispose of any foods that contain beef from a specified European country of origin' (McNiece 2001). Accordingly, ANZFA has also recommended that consumers check the labels on any imported foods they have and discard corned beef, luncheon meat, frankfurters and other products that contain beef with a European country of origin. **This 'suspension' is currently voluntary; it refers only to products originating from European countries (even though other countries could have undetected BSE); there are no stated audit procedures to ensure compliance with the suspensions.** Moreover, at present, the average Australian consumer is unlikely to be aware of any of these recommendations. However, ANZFA is now undertaking a BSE risk assessment (to be completed by October 2001) and has established a committee of international and domestic experts to assist in an assessment of the risk of our having BSE contaminated food products in Australia. In response to this assessment, risk management procedures will presumably be implemented some time in the future, and some public education will be undertaken.

Quarantine regulations prevent air and sea travellers from bringing potentially infected foods into Australia, although the quantities of at risk food confiscated from air passengers, despite the quarantine warnings, is quite remarkable. It is a potential avenue for importation of BSE infection.

The *Australian Consumers' Association* (ACA 2001) has suggested further precautionary actions we should implement:

- publically list potentially contaminated brands and product names
- improve 'country of origin' labeling
- ban import of all beef-derived products from Europe (such as gelatine, tallow, rennet or milk products)
- ban the use of meat and bone meal from **all** animal feedstuffs used in Australia

Table 1 Numbers of cattle in Australia examined post mortem for symptoms of BSE after meeting certain neurological criteria (yearly totals) (D. Adams, pers. comm.)

	State	AQIS	Total
Qld	125	31	156
NSW	80	20	100
Vic	55	13	68
Tas	10	2	12
SA	13	3	16
WA	19	5	24
NT	19	5	24
Totals	321	79	400

- separate the responsibilities of agriculture and health ministers
- involve consumers in open and transparent discussions.

The last point is worth emphasizing. By keeping issues related to the possible effects of CJD and BSE before the public, we have the ‘eyes of the public’ to help police the small percentage of unprincipled individuals who would, for economic or other reasons, be prepared to break the rules in ways that could lose us our ‘clean, green’ BSE-free status. (We would do well to remember the embarrassing ‘roo in the stew’ scandal in the mid 1980s when Australia was found to be exporting horse, buffalo and kangaroo to the USA labeled as ‘Australian beef’. Last month, we learnt that one operator, with falsified documents, moved Johne’s disease infected sheep from southern Australia to southern Queensland, risking infection of all sheep in that state.) A sensitive immunoassay for the detection of MBM contamination of animal feeds that have been heated to temperatures in excess of 130°C has been developed by MAFF (Ansfield 1994) and has since been modified to also detect porcine proteins. **Similar tests or alternative tests (e.g. DNA based) for feed contamination need to be evaluated for use in Australia.**

Governmental conflicts of interest

In the UK, food and agriculture were regulated by the same government department, the Ministry of Agriculture, Fisheries and Food (MAFF). The Phillips’ BSE Inquiry identified a conflict of interest between the roles of promoting agricultural production and protecting consumers with effective food standards. In Australia, we have a Federal Government Department, Agriculture, Fisheries and Food Australia, AFFA, with a similar purview. *Choice Magazine* (ACA 2001) has argued ‘As the UK experience shows, agricultural interests have no place in determining public health decisions in food regulation’. On the other hand, AFFA–BSE (2001) seems to contend that ‘animal health’ and ‘food safety’ are related management issues that can be handled conjointly.

vCJD in Australia

It seems likely that the first cases of vCJD in Australia will most probably occur first in people who have lived in Britain or Europe during the BSE epidemics. However, the possibility that many other countries may now have undetected BSE and contaminated food chains means that tourists visiting other overseas countries could still become infected further into the future. The likelihood of people contracting vCJD from within Australia currently seems low. However, if vCJD did

enter the Australian population, preclinical (asymptomatic) carriers could contaminate blood supplies, surgical instruments or even pass infection in donated organs or tissues—if the experience with sporadic CJD is any indication (Manuelidis 1997)—allowing wider spread of the disease.

In this connection, there is a small risk that some Australians might already be infected from imported products entering Australia, or from eating infected cattle products during overseas trips. Moreover, people could still become infected via imported meat products, so-called ‘health’ foods, vaccines, or other medicines that use bovine extracts in their manufacture. Blood has not been demonstrated to transfer infection in humans and the probability of contracting vCJD infection via blood transfusion must be exceedingly low even though potential donors who have spent time in the UK during the height of the BSE epidemic (1980–1996) are no longer permitted to give blood in Australia. **These bans should be included to include all European travellers.**

The possibility that **infection might be transferred via an Australian organ donor, silently incubating vCJD acquired while overseas, to an unsuspecting recipient probably poses a higher theoretical risk than blood and this possibility should be kept under review.**

A draft contingency plan for the appearance of cases of vCJD in Australia has been prepared for DHAC (see AFFA–BSE 2110). In an editorial in the *Australian Medical Journal* in February 2001, Professor Colin Masters, Department of Pathology, University of Melbourne listed (Masters 2000) what he considered to be imperatives for Australia:

- **ensure all reasonable precautions for risk management are in place and communicated to the public**
- **encourage research into better methods of diagnosis of vCJD and therapeutic strategies**
- **maintain vigilant surveillance of all forms of CJD and create a database in the expectation that epidemiological risk factors will emerge**
- **learn from the hard lessons of our EC colleagues.**

A National CJD Registry has been set up in the same department. The Registry will review cases of sporadic CJD in Australia, provide clinical tests for spinal fluid, tonsil and other lymphoid tissues, and also tests of genetic susceptibility.

Epilogue

Economic considerations often cloud moral judgments. After MBM was banned for use in feedstuffs in Britain, British countries continued to export it to overseas

countries. Currently, European beef banned for sale in Europe because of its likely contamination with BSE is currently being purchased inexpensively by North Korea to help feed its starving people. For the Koreans it is a question of whether people will die of starvation this year, or will live some years then perhaps die from the terrible consequences of vCJD. For people who are not moved by the moral dilemma, there is also the pragmatic consequence that BSE could be spread more widely around the globe. Free trade agreements and threats of retaliatory bans in response to import restrictions on beef products can distort political thinking and could encourage politicians to allow the importation of potentially infective materials from 'at risk' countries.

The current evidence points to the very real possibility of a global pandemic of BSE and its associated human form of vCJD. Numerous EC countries have now confirmed they have BSE in their cattle. The EC believes that BSE is 'highly likely' in 6 candidates for EC membership, viz. Poland, Hungary, Slovakia, Cyprus, Estonia and the Czech Republic. Beyond Europe, the EC believes BSE 'cannot be excluded' in India, Pakistan, Mauritius and Columbia and this month (May 2001) is assessing 17 more countries including China, Thailand and Israel.

Realising that is too late to prevent vCJD from entering the human population, scientists are turning their attention to finding ways of curing people who are infected with vCJD or prolonging their quality of life. Thompson (2001) outlines some of the issues that should be accorded increasingly urgent priority for scientific endeavour. In particular, scientists need to produce reliable diagnostic tests to detect both BSE in cattle and vCJD in humans in the pre-clinical stages. Currently, there are several different types of tests under evaluation, but none that is yet without serious limitations. These tests are urgently required to help us to gauge the extent of the BSE epidemic and its possible human counterpart. One (albeit imperfect) test for BSE-infected meat became mandatory in the EC in January and by March had been credited with keeping the meat from 38 BSE-infected cows off supermarket shelves.

Finally, the BSE epidemic and its vCJD consequences should be viewed in a context as one of a number of pressing medical issues. Other current public health concerns of similar dimensions might include the Aids-HIV epidemic, the increase in malarial drug resistance, and the antibiotic resistance of some of our major bacterial pathogens (e.g. tuberculosis); for example, over the next 15 years when vCJD is likely to be a problem, 10% of the British population can be expected to develop cancer. In the same period, even with a pessimistic prediction, vCJD will probably only cause the deaths of 1–2% of the population. The important difference is, of course, that people can avoid smoking and other predisposing factors for cancer, and many cancers are treatable or curable whereas, currently, vCJD is invariably fatal and strikes down younger rather than older people.

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