

Creekstone Farms Premium Beef v. USDA  
Civ. Action No. 06-544 (JR)  
Plaintiff's Summary Judgment Reply and Opposition

## EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA

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CREEKSTONE FARMS PREMIUM BEEF, LLC,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	Civil Action No. 06-544 (JR)
	)	
UNITED STATES DEPARTMENT OF AGRICULTURE,	)	
and MIKE JOHANNNS, IN HIS CAPACITY AS THE	)	
SECRETARY OF AGRICULTURE,	)	
	)	
Defendants.	)	

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**DECLARATION OF PAUL W. BROWN, M.D.**

Paul W. Brown, MD, certifies and states as follows:

1. My entire 43-year career has been devoted to the study of the Transmissible Spongiform Encephalopathies (TSEs, or ‘prion diseases’) in the National Institutes of Health (NIH) laboratory of Nobel Laureate D. Carleton Gajdusek; and for the last 15 years of my career I held the position of Senior Investigator at the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH. In this capacity I oversaw and conducted research involving these invariably fatal, neurodegenerative diseases, which include both bovine spongiform encephalopathy (BSE), commonly referred to as “mad cow” disease, and variant Creutzfeldt-Jakob Disease (vCJD), a human TSE infection acquired by the consumption of BSE-contaminated meat products.

2. Since leaving the NIH two years ago, I have continued to engage in research, writing, and scientific advisory activities in various aspects of TSE. Ongoing research projects include an ultra-high pressure methodology to inactivate the agent of BSE; a pre-clinical diagnostic blood screening test for TSEs in general, and variant CJD in particular; and a study to determine whether

blood infectivity in humans with CJD can be diluted to extinction (important in the context of the size of plasma pools used for the extraction of therapeutic proteins such as anti-hemophilic factor). I have continued to participate in scientific advisory boards, including chairing the safety committee of LFB (the plasma fractionator in France), co-chairing the scientific research committee of a pharmaceutical consortium to award research contracts, and advising the EuroCJD committee on global BSE and CJD surveillance, and the Argentine Agriculture Department on BSE issues. I have also continued to accept invitations to chair and/or lecture at numerous scientific meetings on TSEs in the Americas and Europe.

I am a member of the American College of Physicians, the American Epidemiological Society, the Infectious Diseases Society of America, the American Society for Virology, the Société Française de Neurologie, and the American Neurological Association. I have authored or co-authored nearly 400 papers, mainly dealing with TSE, and especially the topics of epidemiology, infectivity, and inactivation. (A list of scientific papers (published from 1991 to the present or that are in press) of which I am an author, primarily regarding TSEs, is attached as Attachment A.) Since 1990, I have been an Associate Editor of the European Journal of Epidemiology, and from 1991 until 1997, was an Associate editor of the Journal of the Neurological Sciences.

3. Before entering the NIH in the US Public Health Service, I attended Harvard College (A.B., Magna cum Laude), and the Johns Hopkins School of Medicine (M.D., Alpha Omega Alpha Honor Society), and undertook Medical Internship and Residency training at both the Johns Hopkins Hospital in Baltimore, Maryland, and the University of California School of Medicine in San Francisco, California. I am a Diplomate of the American Board of Internal Medicine. (My curriculum vitae is attached to this declaration as Attachment B.)

4. At the request of William L. Miller of the William Miller Group, PLLC (outside counsel for Creekstone Farms Premium Beef, LLC), on October 11, 2004, I agreed to prepare this declaration regarding the current scientific understanding of bovine spongiform encephalopathy (BSE) in support of the litigation by Creekstone Farms Premium Beef, LLC to be allowed to voluntarily test for BSE in cattle processed at its plant in Arkansas City, Kansas. Prior to October 11, I have had no relationship with Creekstone Farms. The opinions expressed in this declaration are based solely on my knowledge of BSE and other TSEs that I have gained from my experience as a physician and neuroscientist over the past 45 years.

5. Based on current science, we do not know with certainty how far in advance of displaying clinical signs of BSE a bovine animal could test positive using a BSE rapid test such as the rapid test technology developed by Bio-Rad Laboratories, Inc., and currently used by the United States Department of Agriculture to test for BSE. For example, the Canadian Food Inspection Agency (CFIA) recently issued a report on a 50-month-old cow from Alberta, Canada that on July 13, 2006 was confirmed as BSE-infected. The CFIA reports states as follows:

This animal was detected and diagnosed with BSE during a pre-clinical phase of the disease. The normal disease course to expression of clinical signs in this animal would be expected to have included an additional three to six months of incubation followed by an additional one to two months of clinical expression prior to being recognized as symptomatic of BSE and targeted for testing. Had an unrelated disease not hastened her entry into the surveillance stream, this animal would most likely have demonstrated clinical signs sometime between 54 and 56 months, not significantly different from the age range of previous cases.

Canadian Food Inspection Agency, Report On The Investigation Of The Seventh Case Of Bovine Spongiform Encephalopathy (BSE) In Canada, available at

<http://www.inspection.gc.ca/english/anima/heasan/disemala/bseesb/ab2006/7investe.shtml>.

Thus, in this instance, had the cow not succumbed to an unrelated disease and had a brain stem sample submitted for BSE testing, it would probably have been four to eight months longer before the cow would have displayed symptoms that might have caused it to be tested because of suspicion of BSE.

6. Experimental studies to determine range of intervals between positive tests and the onset of clinical signs have not been done (a critical experiment has in fact been done in the UK, but only infectivity was measured, and tests for the presence of prion protein have not been done). Wells, G. A. H., S.A. Hawkins, R.B. Green, A.R. Austin, I. Dexter, Y.I. Spencer, M.J., Chaplin, M.J. Stack, and M Dawson, 1998, Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update, *Vet. Rec.* 142:103-106; Wells, G.A.H., J. Spiropoulos, S.A.C. Hawkins, and S. J.Ryder, 2005, Pathogenesis of experimental bovine spongiform encephalopathy: preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle, *Vet. Rec.* 156:401-407. Equally important, field experience in countries that have gone to universal testing (including universal testing above a certain age) has shown that such testing (active surveillance) identifies considerably more cases than only testing cattle whose behavior happens to attract the attention of authorities happens to attract the attention of authorities (passive surveillance).

Report on the Monitoring and Testing of Ruminants for the Presence of Transmissible Spongiform Encephalopathy (TSE) in the EU in 2005, Final Annual Report, 2005, European Commission, 20 June 2006. (Section 4.2, Chart B2), available at

[http://ec.europa.eu/food/food/biosafety/bse/annual\\_reps\\_en.htm](http://ec.europa.eu/food/food/biosafety/bse/annual_reps_en.htm).

7. Assumptions about the likely course of BSE infection in cattle and its significance for potential vCJD infection in humans who consume cattle tissues are largely just that—assumptions or extrapolations from limited data, not tested conclusions. We have little or no direct evidence of such things as when in life a bovine is most susceptible to BSE; how much less susceptible, if at all, humans are than cattle; whether shorter incubation times in cattle are the result of exposure to a high dose at a young age or some other factor(s) (such as genetic susceptibility or the strain of prions); how many humans may ultimately be shown to have vCJD; or how effective SRM removal is at reducing the risk of transmission of BSE from an infected animal.

8. The question of the interval between when cattle may test positive for BSE and when those cattle exhibit clinical signs of the disease has in any case been made irrelevant by the recent discovery of atypical cases of BSE that usually occur in older asymptomatic animals that for one reason or another are culled, and are then discovered to test positive. Thus, some cattle that on visual inspection appear normal are infected, and this fact negates any argument about a limited window of 'pre-clinical' positivity in BSE tests, as there are no signs leading to a suspicion of infection. The *only* way that these cattle are identified as BSE-infected is through testing. The frequency of such infections is not yet known, but so far has ranged from less than 1% all the way up to 15% of the total number of test positives. International Conference on Prion Diseases of NeuroPrion, Network of Excellence, Prion2006, Turin, Italy, 4-6 October 2006, Book of Abstracts (hereinafter "Prion2006 Abstracts"), *See* [http://www.neuroprion.com/en/ev\\_prion2006.html](http://www.neuroprion.com/en/ev_prion2006.html); Brown P, McShane LM, Zanusso G, Detwiler L, On the question of sporadic or atypical bovine spongiform encephalopathy and

Creutzfeldt-Jakob disease, *Emerg. Inf. Dis.*, 2006, 12: 1816-21, in press, December 2006. (A copy of the article is attached to this declaration as Attachment C.)

9. Although these cases of asymptomatic, atypical BSE have been found in older cattle, we do not currently know the concentration and distribution of infection and infectivity that might have been found in these cattle at an earlier age. Another issue concerns evidence that atypical BSE may be more virulent for humans than typical BSE. This evidence comes from experimental transmission studies in at least 4 different laboratories. All have shown more rapid onset of disease (shorter incubation periods) following inoculation with atypical BSE than with typical BSE, and in one study, BSE did not transmit at all. These studies involved the use of wild-type mice, bovinized and humanized transgenic mice, and (most worrisome) non-human primates as recipient animals. Prion2006 Abstracts, *See* [http://www.neuroprion.com/en/ev\\_prion2006.html](http://www.neuroprion.com/en/ev_prion2006.html).

10. We do not have any direct evidence of how few BSE prions need to be consumed in order for a human to be at risk of vCJD. Just because the disease has not progressed far enough in a bovine to produce clinical symptoms does not mean that there are insufficient concentrations of BSE prions in that bovine's tissue to present a risk of vCJD if consumed. (In fact, logic suggests the contrary, because it would imply that all of the people with vCJD were infected by the consumption of meat products from cattle that were displaying signs of BSE at the time of slaughter, which seems highly unlikely.) The available tests for BSE are generally believed to have lower limits of detecting concentrations of prions that, if ingested, could cause BSE in other cattle, or potentially vCJD in humans. In cattle, the minimum amount of tissue needed to infect a cow by the oral route is only 0.001 gram (Dr. Gerald Wells, personal

communication), and this figure has been used for risk analyses in humans (a hypothesized bovine to human 'species barrier' effect has never been documented).

11. Just because cattle are under 30 months of age does not mean that they present no risk of BSE, both because of the facts discussed above about the uncertain relationship between testing positive for BSE and having sufficiently concentrated prions to cause infection in humans, and because BSE has been detected in younger cattle in Europe and Japan. Additionally, the way that the age of cattle to be slaughtered is often determined (dentition) is not very precise. As a matter of protecting animal and human health from the fatal consequences as BSE, detecting even a handful of cases that otherwise would be missed is very valuable. USDA requires testing of agricultural products for numerous diseases which are (thankfully) extremely rare, such as *E. coli*.

12. The USDA has performed BSE tests on thousands of cattle younger than 30 months, including thousands that had no clinical signs of BSE.

13. Measures that the United States (and Canada) has put in place to reduce the transmission of BSE have substantially reduced the risk in the United States, but have not eliminated it. Experience has shown that the feed bans are incomplete, both because the bans are limited and because of imperfect implementation.

14. Collecting additional BSE test data from cattle less likely to have detectable levels of BSE (because they are younger and do not display other risk factors), while not as cost-effective, is not worthless and produces data that could help better understand BSE and its distribution in U.S. cattle. (For example, if authorities only tested cattle suspected of having BSE, the Canadians would not have found BSE in the 50 month old Alberta cow that did not have outward signs that might have suggested BSE and was born long after exposure to BSE in

cattle feed was believed to have ceased; nor is it likely that either of the two indigenously infected US cows with atypical BSE that tested positive would have been identified.) Evolving knowledge about atypical BSE, where there are only rarely outward signs that might cause the animal to be singled out and tested based on suspicion of BSE, makes the value of testing asymptomatic cattle even clearer. Voluntary testing does not interfere with or dilute government efforts to test for BSE and to understand the disease. Additionally, while most cattle slaughtered in the U.S. are under 30 months of age, many thousands every year are over 30. I am not aware of any other programs under which USDA has prohibited testing for a disease because it is unlikely that the disease will be found.

15. The USDA recently announced a dramatic (ten-fold) reduction in the number of cattle it will test for BSE. USDA plans to reduce the current annual rate of over 400,000 cows to only 40,000 (less than 1 % of the cattle that are slaughtered or die each year). USDA News Release No. 0255.06, July 20, 2006, available at [http://www.usda.gov/wps/portal/!ut/p/\\_s.7\\_0\\_A/7\\_0\\_1OB?contentidonly=true&contentid=2006/07/0255.xml](http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?contentidonly=true&contentid=2006/07/0255.xml). Preventing voluntary testing while at the same time dramatically reducing government testing does not make any sense for the protection of animal and human health and is further indication that voluntary BSE testing is not "worthless." Although the USDA and the OIE have stated that targeted testing of cattle most likely to have BSE is the most effective way of detecting and monitoring BSE infection in a country's cattle herd, most developed countries known to have BSE nonetheless have chosen to go far beyond such targeted testing in their domestic BSE monitoring programs, especially in view of the growing proportion of infected cattle that have atypical (and asymptomatic) forms of BSE when slaughtered.

16. BSE tests do not involve the immune system of the animal that is tested. There is a sharp distinction between using immunological means to prevent foreign pathogen infections (e.g., active and passive immunization) and the use of an immunologic reagent (e.g., an antibody) to detect infectious prion proteins obtained from the body of an infected host. The use of such a test has nothing whatsoever to do with the immune system of the infected (and now dead) animal. USDA thinking on this point is very confused.

17. The USDA allows suppliers of meat and other products to certify that those products meet criteria unrelated to food safety (or least, where USDA does not have data to conclude that there is a food safety benefit). I believe this is true, for example, of "organic," "natural," "hormone-free," "grass-fed," and other descriptors that USDA allows. Given the legitimate role of the USDA to protect consumers from industry incompetence, it nevertheless seems unreasonable for USDA to prohibit the private use of its own validated test method. The desire on the part of some consumers to have a higher standard of safety with respect to what they eat should not be circumvented by this kind of attitude, even if most people are satisfied with government assurances of safety based on its own evaluation.

I declare under penalty of perjury that the foregoing is true and correct.

A handwritten signature in black ink that reads "Paul Brown MD". The signature is written in a cursive, somewhat stylized font.

Paul Brown, M.D.

Executed on October 27, 2006.

ATTACHMENT A

Paul W. Brown, M.D.  
List of Publications 1991 to Present

**Paul W. Brown, M.D.**

## LIST OF PUBLICATIONS 1991 TO PRESENT

1991

153. Goldfarb, L.G., Brown, P. and Gajdusek, D.C. Multiple mutations in kuru, Creutzfeldt-Jakob disease, and Gerstmann-Sträussler syndrome. *Brain Research*, 16: 1 (January), 98-99, 1991.
154. Brown P. and Gajdusek, D.C. New studies on the resistance of scrapie agent to enzymatic digestion, heat and chemical denaturation, and natural weathering. *Brain Research*, 16: 1 (January), 100-103, 1991.
155. Brown, P. and Gajdusek, D.C. Survival of scrapie virus after 3 years' interment. *Lancet*, 337: 8736 (February 2), 269-270, 1991.
156. Goldfarb L.G., Haltia, M., Brown, P., Nieto, A., Kovanen, J., McCombie, W.R., Trapp, S. and Gajdusek, D.C. New mutation in scrapie amyloid precursor gene (codon 178) in Finnish Creutzfeldt-Jakob kindred. *Lancet*, 337: 8738 (February 16), 425, 1991.
157. Nieto, A., Goldfarb, L.G., Brown, P., McCombie W.R., Trapp, S., Asher, D.M. and Gajdusek, D.C. Codon 178 mutation in ethnically diverse Creutzfeldt-Jakob disease families. *Lancet*, 337: 8741 (March 9), 622-623, 1991.
158. Fradkin, J.E., Schonberger, L., Mills, J.L., Gunn, W.J., Piper, J.M., Wysowski, D.K., Thomson, R., Durako, S. and Brown, P. Creutzfeldt-Jakob disease in pituitary growth hormone recipients in the United States. *Journal of the American Medical Association*, 265: 7 (February 20), 880-884, 1991. Also as abstract:  
Fradkin, J.E., Schonberger, L., Mills, J.L., Gunn, W.J., Piper, J.M., Wysowski, D.K., Thomson, R., Durako, S. and Brown, P. Creutzfeldt-Jakob disease in pituitary growth hormone recipients in the United States. In: "Program and Abstracts, The Endocrine Society 72nd Annual Meeting, Atlanta, GA, June 20-23, 1990, p. 350.
159. Brown, P., Goldfarb, L.G., Brown, W.T., Goldgaber, D., Rubenstein, R., Kascsak, R. J., Piccardo, P., Boellaard, J.W. and Gajdusek, D.C. Clinical and molecular genetic study of a large German kindred with Gerstmann-Sträussler-Scheinker syndrome. *Neurology*, 41: 3 (March), 375-379, 1991.
160. Brown, P., Goldfarb, L.G. and Gajdusek, D.C. The new biology of spongiform encephalopathy: infectious amyloidoses with a genetic twist. *Lancet*, 337: 8748 (April 27), 1019-1022, 1991.
161. Pocchiari, M., Peano, S., Conz, A., Eshkol, A., Maillard, F., Brown, P., Gibbs, C.J., Jr., Geng Xi, Y., Tenham-Fisher, E. and Macchi, G. Combination ultrafiltration and 6 M urea treatment of human growth hormone effectively minimizes risk from potential Creutzfeldt-Jakob disease virus contamination. *Hormone Research*, 35: 3-4 (March-April), 161-166, 1991.

1991 (Con't.)

162. Brown, P., Goldfarb, L.G., Gibbs, C.J., Jr. and Gajdusek, D.C. The phenotypic expression of different mutations in transmissible familial Creutzfeldt-Jakob disease. *European Journal of Epidemiology*, 7:5 (September), 469-476, 1991.
163. Goldfarb, L.G., Brown, P., Mitrová, E., Haltia, M., Cervenáková, L., Goldin, L., Korczyn, A., Chapman, J., Galvez, S., Cartier, L., Rubenstein, R. and Gajdusek, D.C. Familial Creutzfeldt-Jakob disease associated with the PRNP codon 200<sup>LYS</sup> mutation: an analysis of 45 families. *European Journal of Epidemiology*, 7:5 (September), 477-486, 1991.
164. Mitrová, E., Brown, P., Hroncová, D., Tatara, M. and Zilák, J. Focal accumulation of CJD in Slovakia: retrospective investigation of a new rural familial cluster. *European Journal of Epidemiology*, 7:5 (September), 487-489, 1991.
165. Haltia, M., Kovanen, J., Goldfarb, L.G., Brown, P. and Gajdusek, D.C. Familial Creutzfeldt-Jakob disease in Finland: epidemiological, clinical, pathological and molecular genetic studies. *European Journal of Epidemiology*, 1991, 7:5 (September), 494-500, 1991. Also as abstracts:  
Haltia, M., Kovanen, J., Goldfarb, L.G. and Gajdusek, D.C. Novel mutation in the PRNP amyloid precursor gene co-segregates with Creutzfeldt-Jakob disease in a Finnish family. Abstracts of the 36th Annual Meeting of the Deutsche Gesellschaft für Neuropathologie und Neuroanatomie Düsseldorf, September 16-18, 1991. *Clinical Neuropathology*, 10: 5 (September/October), 257, 1991  
Haltia, M., Kovanen, J., Goldfarb, L.G., Brown, P. and Gajdusek, D.C. A new mutation (at codon 178) in the PRNP amyloid precursor gene co-segregates with Creutzfeldt-Jakob disease in a large Finnish kindred. Abstracts of the First Hungarian Conference of Neuropathology and the 5th Hungarian-Polish Neuropathological Symposium, Budapest, September 26-28, 1991. *Ideggyógyászati Szemle (Neurological Review)*, 44 (Suppl. 1), 35, 1991.
166. Liberski, P.P., Kwiecinski, H., Barcikowska, M., Mirecka, B., Kulczycki, J., Kida, E., Brown, P. and Gajdusek, D.C. PrP amyloid plaques in Creutzfeldt-Jakob disease of short duration: immunohistochemical studies of 5 cases from Poland. *European Journal of Epidemiology*, 7:5 (September), 505-510, 1991.
167. Brown, P. The clinical epidemiology of Creutzfeldt-Jakob disease in the context of bovine spongiform encephalopathy. In: "Sub-acute Spongiform Encephalopathies", R. Bradley, M. Savey and B.A. Marchant, editors. Kluwer Academic Publishers, Dordrecht (The Netherlands), 1991, pp.195-202.
168. Brown, P. and Gajdusek, D.C. The human spongiform encephalopathies: kuru, Creutzfeldt-Jakob disease, and the Gerstmann-Sträussler-Scheinker syndrome. In: "Transmissible Spongiform Encephalopathies: Scrapie, BSE and Related Disorders", B.W. Chesebro, editor. *Current Topics in Microbiology and Immunology*, volume 172, Springer Verlag, Berlin, 1991, pp.1-20.

1991 (Con't.)

169. Brown, P. Molecular genetics of spongiform encephalopathy. *Neuroscience Facts*, 2:19 (October 3), 2, 1991.
170. Brown, P., Goldfarb, L.G., Cathala, F., Vrbovska, A., Sulima, M., Nieto, A., Gibbs, C.J., Jr. and Gajdusek, D.C. The molecular genetics of familial Creutzfeldt-Jakob disease in France. *Journal of the Neurological Sciences*, 105:2 (October), 240-246, 1991.
171. Scrimgeour, E.M. and Brown, P. BSE and potential risks to slaughtermen. *Veterinary Record*, 129: 17 (October 26), 390-391, 1991.
172. Liberski, P.P., Brown, P., Shu-Yan, X. and Gajdusek, D.C. The ultrastructural diversity of scrapie-associated fibrils isolated from experimental scrapie and Creutzfeldt-Jakob disease. *Journal of Comparative Pathology*, 105:4 (November), 377-386, 1991.
173. Trabattoni, G., Lechi, A., Bettoni, L., Macchi, G., Masullo, C., Brown, P. and Pocchiari, M. Creutzfeldt-Jakob disease in Italy (letter to the editor). *European Journal of Epidemiology*, 7: 6 (November), 713-714, 1991.
174. Goldfarb, L.G., Brown, P., McCombie, W.R., Goldgaber, D., Swergold, G.D., Wills, P.R., Cervenakova, L., Baron, H., Gibbs, C.J., Jr. and Gajdusek, D.C. Transmissible familial Creutzfeldt-Jakob disease associated with five, seven, and eight extra octapeptide coding repeats in the PRNP gene. *Proceedings of the National Academy of Sciences (USA)*, 88:23 (December 1), 10926-10930, 1991.
175. Laplanche, J.-L., Chatelain, J., Thomas, S., Brown, P. and Cathala, F. Analyse du gene PrP dans une famille d'origine Tunisienne atteinte de maladie de Creutzfeldt-Jakob. *Revue Neurologique (Paris)*, 147: 12 (December), 825-827, 1991.
176. Korczyn, A.D., Chapman, J., Goldfarb, L.G., Brown, P. and Gajdusek, D.C. A mutation in the prion protein gene in Creutzfeldt-Jakob disease in Jewish patients of Libyan, Greek, and Tunisian origin. *Annals of the New York Academy of Sciences*, 640:(December 3), 171-176, 1991.

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178. Goldfarb, L.G., Brown, P., Haltia, M., Cathala, F., McCombie, W.R., Kovanen, J., Goldin, L., Nieto, A., Godec, M.S., Asher, D.M. and Gajdusek, D.C. Creutzfeldt-Jakob disease co-segregates with the codon 178<sup>Asn</sup> PRNP mutation in families of European origin. *Annals of Neurology*, 31:3 (March), 274-281, 1992.

1992 (Con't.)

179. Brown, P., Goldfarb, L.G., Kovanen, J., Haltia, M., Cathala, F., Sulima, M., Gibbs, C.J., Jr. and Gajdusek, D.C. Phenotypic characteristics of familial Creutzfeldt-Jakob disease associated with the codon 178<sup>Asn</sup> mutation. *Annals of Neurology*, 31:3 (March), 282-285, 1992.
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181. Chapman, J., Brown, P., Rabey, M.J., Goldfarb, L.G., Inzelberg, R., Gibbs, C.J., Jr., Gajdusek, D.C. and Korczyn, A.D. Transmission of spongiform encephalopathy from a familial Creutzfeldt-Jakob disease patient of Jewish Libyan origin carrying the PRNP codon 200 mutation. *Neurology*, 42:6 (June), 1249-1250. 1992. Also as abstract: Brown, P., Goldfarb, L.G., Gibbs, C.J., Jr., Gajdusek, D.C., Chapman, J., Rabey, M.J., Inzelberg, R. and Korczyn, A.D. Transmission of spongiform encephalopathy from a Creutzfeldt-Jakob disease (CJD) patient of Jewish Libyan origin carrying the PRNP codon 200 mutation. Abstract no. 781S in: "American Academy of Neurology 44th Annual Meeting", San Diego, May 3-9, 1992. *Neurology*, 42:4 (April), Supplement 3, 370, 1992.
182. Brown, P., Preece, M.A. and Will, R.G. "Friendly fire" in medicine: hormones, homografts, and Creutzfeldt-Jakob disease. *Lancet*, 340:8810 (July 4), 24-27, 1992.
183. Goldfarb, L.G., Brown, P., Vrbovska, A., Baron, H., McCombie, W.R., Cathala, F., Gibbs, C.J., Jr. and Gajdusek, D.C. An insert mutation in the chromosome 20 amyloid precursor gene in a Gerstmann-Sträussler-Scheinker family. *Journal of the Neurological Sciences*, 111:2 (September), 189-194, 1992.
184. Brown, P., Gálvez, S., Goldfarb, L.G., Nieto, A., Cartier, L., Gibbs, C.J., Jr. and Gajdusek, D.C. Familial Creutzfeldt-Jakob disease in Chile is associated with the codon 200 mutation of the PRNP amyloid precursor gene on chromosome 20. *Journal of the Neurological Sciences*, 112:1,2 (October), 65-67, 1992.
185. Goldfarb, L.G., Petersen, R.B., Tabaton, M., Brown, P., LeBlanc, A.C., Montagna, P., Cortelli, P., Julien, J., Vital, C., Pendelbury, W.W., Haltia, M., Wills, P.R., Hauw, J.J., McKeever, P.E., Monari, L., Schrank, B., Swergold, G.D., Autilio-Gambetti, L., Gajdusek, D.C., Lugaresi, E. and Gambetti, P. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. *Science*, 258:5083 (October 30), 806-808, 1992. Also as abstract: Petersen, R.B., Goldfarb, L., Tabaton, M., Brown, P., LeBlanc, A., Montagna, P., Cortelli, P., Monari, L., Autilio-Gambetti, L., Gajdusek, D.C., Lugaresi, E. and Gambetti, P. Fatal familial insomnia and one subtype of familial Creutzfeldt-Jakob disease: effect of a polymorphism on a pathogenic mutation in the prion protein. *The FASEB Journal*, 7: 4 (February 23), A627, 1993.

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186. Bertoni, J.M., Brown, P., Goldfarb, L.G., Rubenstein, R. and Gajdusek, D.C. Familial Creutzfeldt-Jakob disease (codon 200 mutation) with supranuclear palsy. *Journal of the American Medical Association*, 268:17 (November 4), 2413-2415, 1992.
187. Goldfarb, L.G., Brown, P. and Gajdusek, D.C. The molecular genetics of human transmissible spongiform encephalopathy. In: "Prion Diseases of Humans and Animals", S.B. Prusiner, J. Collinge, J. Powell and B. Anderton, editors, Ellis Horwood, Chichester (England), 1992, pp.139-153.

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188. Brown, P. The molecular biology and genetics of spongiform encephalopathy. In: "Light and Electron Microscopic Neuropathology of Slow Virus Disorders", P.P. Liberski, editor. CRC Press, Boca Raton, Florida, 1993, pp.63-100.
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ATTACHMENT B

Paul W. Brown, M.D.  
Curriculum Vitae

**Paul W. Brown, M.D.**

**CURRICULUM VITAE**

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Education and experience A.B. (Magna cum Laude), Harvard College, 1957  
M.D., The Johns Hopkins School of Medicine, 1961

Internship and 1st year medical residency:  
Osler Medical Service, The Johns Hopkins Hospital,  
1961-1963

Research Associate, NINDS, NIH, 1963-1965.

Staff Associate, National Institute of Child Health and  
Human Development, (NICHD), NIH, 1965-70  
2nd year medical residency, University of California San  
Francisco Medical Center, 1965-66  
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The Johns Hopkins Hospital, 1966-67  
Chargé de Recherche, L'Institut National de la Santé et de  
la Recherche Médicale (INSERM), and Medical  
Consultant, American Embassy, Paris, 1971-72

Staff Associate, NINDS, NIH, 1971-89  
Visiting Scientist, INSERM, Laboratoire de  
Neurovirologie, Clinique des Maladies du Système  
Nerveux, Hôpital de la Salpêtrière, Paris, 1977-78

Medical Director, US Public Health Service, 1979-1999  
Senior Investigator, NINDS, 1990-2004

Society affiliations American College of Physicians  
American Epidemiological Society  
Infectious Diseases Society of America  
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Languages	English and French
Publications	Over 380 papers during a span of 40 years, mainly dealing with transmissible spongiform encephalopathy (TSE), and especially the topics of epidemiology, infectivity, and inactivation
Editorial positions	European Journal of Epidemiology, Associate editor, 1990- Journal of the Neurological Sciences, Associate editor, 1991-97
Honors and recognitions	<ul style="list-style-type: none"> <li>- Henry Strong Denison Scholar, The Johns Hopkins School of Medicine, 1961</li> <li>- Alpha Omega Alpha (AOA), Johns Hopkins Chapter, 1961</li> <li>- Diplomate, American Board of Internal Medicine, 1968</li> <li>- Prix Léopold Trasbot, Académie Vétérinaire de France, 1980</li> <li>- Fellow, National Multiple Sclerosis Society, 1971-72</li> <li>- Fellow, Committee to Combat Huntington's Chorea, 1973</li> <li>- Chairman, DHHS Interagency Epidemiology Subcommittee on Human Growth Hormone and</li> </ul>
Creutzfeldt-Jakob disease,	1985 to present
1992 to present	<ul style="list-style-type: none"> <li>- Lawson Wilkins Pediatric Endocrine Society Lecture, Los Angeles, California, 1987</li> <li>- Thomas Campione Lecture, Northwestern University School of Medicine, 1987</li> <li>- USPHS Commendation Medal, 1990</li> <li>- Arnold Barnett Lecture, Wichita Society of Neuroscience, 1991</li> <li>- Member, WHO Expert Advisory Panel on Neurosciences, 1991-1993</li> <li>- Consultant to PAHO (Pan American Health Organization) for the evaluation of bovine spongiform encephalopathy in Latin America, 1992</li> <li>- USPHS Outstanding Service Medal, 1992</li> <li>- Consultant to EEC Biomed 1/2 Project: Surveillance of Creutzfeldt-Jakob disease in the European Community,</li> </ul>
	<ul style="list-style-type: none"> <li>- Andrew Mark Lippard Memorial Lecture, College of Physicians and Surgeons of Columbia University, 1995</li> <li>- Chairman, WHO consultation on TSE and Medical Products (1997)</li> <li>- Transmissible Spongiform Encephalopathies Advisory Committee, Center for Biologics Evaluation and Research, FDA: Chairman 1997-2001; Ad hoc member 2001-present</li> <li>- Chairman, Neurodegenerative Diseases Working Group, World Federation of Scientists, 1998-2000</li> </ul>

Honors and  
recognitions  
(continued)

- Chairman, WHO consultation on TSE and Infection Control Guidelines (1999)
- Distinguished Scientist Seminar Lecturer, University of South Alabama School of Medicine, 2000
- Marie C. and Joseph C. Wilson Memorial Lecture, University of Rochester Medical Center, 2000
- Bill Stone Distinguished Speaker, 2001  
South Texas Blood & Tissue Center
- Convocation Lecture and Seminar, Berea College, 2001
- Fredrich Deinhardt Lectureship, 18<sup>th</sup> Annual Clinical Virology Symposium, Clearwater Beach, Florida, 2002
- Board of Governors and Board of Scientific Directors, The Memorial Institute for Neurodegenerative Diseases of Saskatchewan, Canada, 2003
- Eagleson Lecture, American Biological Safety Association Conference, 2004
- Plenary Lecture, European Network of Excellence Neuroprion Conference, Paris, 2004
- Co-Chairman, Dominique Dormont Memorial Conference, Paris, 2005
- Co-President, Fondation Alliance de Biotechnologie, Paris, 2006 onwards

ATTACHMENT C

Brown, P, McShane, LM, Zanusso, G, Detwiler, L, On the question of sporadic or atypical bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jakob disease

# On the Question of Sporadic or Atypical Bovine Spongiform Encephalopathy and Creutzfeldt-Jakob Disease

Paul Brown,\* Lisa M. McShane,† Gianluigi Zanusso,‡ and Linda Detwiler§

Strategies to investigate the possible existence of sporadic bovine spongiform encephalopathy (BSE) require systematic testing programs to identify cases in countries considered to have little or no risk for orally acquired disease, or to detect a stable occurrence of atypical cases in countries in which orally acquired disease is disappearing. To achieve 95% statistical confidence that the prevalence of sporadic BSE is no greater than 1 per million (i.e., the annual incidence of sporadic Creutzfeldt-Jakob disease [CJD] in humans) would require negative tests in 3 million randomly selected older cattle. A link between BSE and sporadic CJD has been suggested on the basis of laboratory studies but is unsupported by epidemiologic observation. Such a link might yet be established by the discovery of a specific molecular marker or of particular combinations of trends over time of typical and atypical BSE and various subtypes of sporadic CJD, as their numbers are influenced by a continuation of current public health measures that exclude high-risk bovine tissues from the animal and human food chains.

**B**ovine spongiform encephalopathy (BSE) was first recognized in 1986 in the United Kingdom and quickly reached epidemic proportions, affecting >30,000 cattle per year by 1992. Because of continuing exportation of both live cattle and meat and bone meal rendered from the carcasses of slaughtered cattle, the disease spread throughout most of Europe and a few non-European countries. By 2006, 20 years after its first appearance in the United Kingdom, the disease had been reported in an additional 24 countries (1).

Beginning toward the end of the 1980s in the United Kingdom, and in the 1990s in other countries, numerous regulations were enacted to minimize the entry of contaminated tissues into both the animal and human food chains and to eliminate the international spread of disease. These measures have been extraordinarily successful, to the extent that no new countries have been added to the list during the past year and the number of new cases has dramatically diminished in most countries in which BSE has appeared (the situation in some countries with insufficient surveillance remains unclear).

Although the origin of the epidemic is thought to have been caused by a species-crossing contamination by sheep scrapie during the course of rendering and recycling carcass meat and bone meal as cattle feed, an alternative hypothesis suggested an origin in a similarly recycled case of spontaneously occurring disease in cattle. The pros and cons of these competing ideas have been argued elsewhere (2,3), and neither will ever be convincingly proved or disproved. Thus, the phenomenon of spontaneous disease remained in limbo until the recent discovery of "atypical" strains of BSE reopened the question. In this article we consider the importance of atypical BSE within the overall concept of sporadic (spontaneous) disease and whether such cases, if they exist, could account for at least some cases of apparently sporadic Creutzfeldt-Jakob (CJD) in humans.

## Sporadic BSE

Obviously, the ideal country in which to examine the question of sporadic BSE would have a large national herd that was guaranteed never to have been exposed to environmental sources of infection. Such an ideal will never be realized. Until recently, the United States appeared to have at least approached the ideal by having a large national

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herd, an adequate testing program, and an apparently small risk for contamination by imported cattle or cattle feed. That position was made vulnerable in late 2003 by the discovery of a case of BSE imported from Canada and was eliminated altogether by the subsequent discovery of 2 indigenously infected animals in widely separate regions of the country. Although the 2 indigenously cases might represent sporadic disease, the continuing identification of cases in western Canada, coupled with a history of substantial numbers of cattle imported from Canada into the United States (both indigenously US animals had the same molecular “signature” as the most recent Canadian case), makes it difficult to ignore the possibility of undetected instances of feed contamination from imported and recycled infectious carcasses.

At present, the 2 best countries in which to undertake testing programs would be Argentina and Australia; both have large national herds ( $\approx 50$  million and 30 million animals, respectively), and both are considered to be free of orally acquired BSE infections, on the basis of importation history, nutritional practices, and adequacy of surveillance (4). Even in these countries, however, the discovery of a case of BSE could not be guaranteed to be spontaneous because of the widespread global distribution of potentially infected cattle and cattle feed and the vagaries of international trade: imperfect record keeping, lack of compliance, and just plain deception.

By way of illustration, an incident occurred many years ago that involved a particularly bulky shipment labeled as a pesticide. The large quantity seemed unusual to the customs inspector, who opened it and discovered that the shipment contained meat and bone meal destined to be spread on fields to inhibit grazing by deer, a serious agricultural pest. Thus, a study of sporadic BSE would only be truly convincing if no cases were identified.

Moreover, the criteria for answering the question of sporadic BSE are different than for orally acquired BSE. Most importantly, we do not know at what age sporadic cases of BSE might occur, but they are unlikely to be in the 3- to 5-year-old age group in which orally acquired BSE is most prevalent. If the age distribution of sporadic disease in cattle were to mimic that of sporadic CJD in humans, it would not peak until 14–20 years of age (the last third of the  $\approx 20$ -year natural life span of a cow). Substantial numbers of such older cattle do not exist, and thus it may never be possible to state with assurance that spontaneous BSE does not occur.

Even if we accept this practical constraint, we can still take advantage of the fact that in many countries a proportion of the total slaughter population consists of breeding stock and dairy cows that are culled at  $\geq 7$  years of age, and animals that go directly to rendering plants or die “on farm” further increase this number. Argentina, for exam-

ple, with a national herd of  $\approx 50$  million cattle, in 2005 recorded nearly 1.4 million deaths from slaughter and natural causes in animals  $\geq 7$  years (L. Mascitelli, pers. comm.).

Approximately 10% of cases of sporadic CJD occur in patients 25–50 years of age; this age in humans corresponds to the middle third of a cow’s normal life span, or 7–13 years of age (Figure 1). If the age distribution of sporadic BSE followed the same pattern, negative test results in a total of  $\approx 3$  million animals randomly selected from this group would allow us to be 95% confident that sporadic BSE is not present at a prevalence  $>1$  per million, and  $\approx 4.5$  million negative animals would raise the level of confidence to 99%. Larger numbers of BSE-negative animals would be required to achieve these levels of confidence for a maximum prevalence  $\leq 1$  per 10 million cattle (Table 1, Figure 2).

Even the least rigorous negative result—a prevalence not greater than that of sporadic CJD in humans, or 1 per million—would require several years to achieve, and it is perhaps unrealistic to suppose that the motivation to prolong the testing program will endure much beyond the global disappearance of orally acquired BSE and variant CJD. Nevertheless, to the degree that testing older as well as younger adult animals approached these numbers, both statistical and consumer confidence would increase, and at the very least provide reassurance that the occurrence of sporadic disease must be exceedingly rare, with little likelihood of posing a risk to either human or animal nutrition.

### Atypical BSE

Because of its contemporary nature, the study of atypical BSE is very much a work in progress, with comparatively little published data and many unknowns. The first 2 cases to be identified were a serendipitous discovery made in the course of an unrelated experimental study that required a detailed neuropathologic and immunochemical

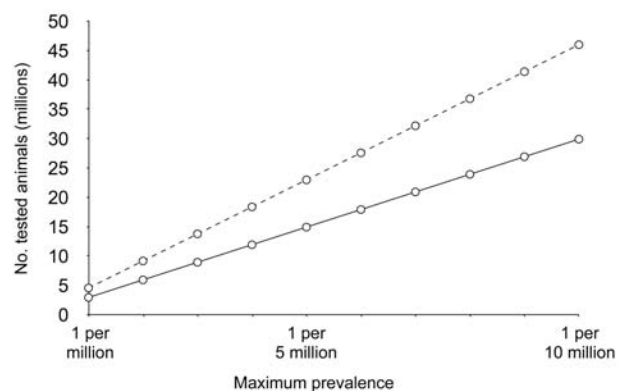


Figure 2. Maximum prevalence according to number of negative cattle at 95% (solid line) and 99% (dashed line) confidence levels. See Table 1 for exact numbers and statistical method.

## PERSPECTIVE

Table 1. Total number of older cattle with negative test results required to achieve 95% or 99% confidence\* that sporadic cases of BSE are not present at a level higher than the illustrated prevalence rates†

Maximum prevalence	Log <sub>10</sub> prevalence	No. tested cattle	
		95% Confidence	99% Confidence
1 per million	-6.000	2,995,731	4,605,168
1 per 2 million	-6.301	5,991,463	9,210,338
1 per 3 million	-6.477	8,987,195	13,815,508
1 per 4 million	-6.602	11,982,928	18,420,678
1 per 5 million	-6.699	14,978,660	23,025,849
1 per 6 million	-6.778	17,974,392	27,631,019
1 per 7 million	-6.845	20,970,124	32,236,189
1 per 8 million	-6.903	23,965,857	36,841,359
1 per 9 million	-6.954	26,961,589	41,446,529
1 per 10 million	-7.000	29,957,321	46,051,700

\* $\alpha = 0.05$  or  $0.01$ .†The required number of tests, all of which must be negative, is given by  $\log(\alpha)/\log(1-\text{prevalence})$ ; BSE, bovine spongiform encephalopathy.

examination of the entire brain (5). The absence of clinical signs in these older animals, the unusual distribution of PrP<sup>TSE</sup>, together with amyloid plaques, and a Western blot pattern that differed from the stereotypic pattern seen in typical BSE left little doubt about the probability that a new “atypical strain” had been identified (bovine amyloidotic spongiform encephalopathy[BASE]).

Although no further cases were found in nearly 200 cattle examined in Italy, the initiation of Western blot studies of animals in other countries with screening test programs began to yield additional atypical patterns (Table 2, Figure 3) (6–14; P. Lind, pers. comm.). Two major patterns have been described, named L (resembling the original Italian case pattern with a lower molecular weight than typical BSE) and H (for a distinct pattern first seen in France with a higher molecular weight than typical BSE). It is not yet clear whether other mixed patterns result from technical procedures in different laboratories or whether a more complicated scheme of classification will evolve as more atypical patterns are discovered.

In addition, Western blots of PrP<sup>TSE</sup> are a fragile basis on which to define a BSE phenotype. Little or no information is available about either the clinical status or neuropathologic features of these animals. We know that cases have occurred in different breeds and PrP genotypes, and we also know that very few of the animals have had the typical clinical picture of BSE (behavioral disturbances, sensory signs, ataxia, and tremors), but a cloud of ambiguity surrounds the clinical picture even in those animals for which an extensive post-hoc investigation was undertaken. The fact that few detailed neuropathologic results are available is explained by the need to preserve at least a full half brain for examination, which is presently not done in any of the various countries that have screening test programs. In the future, the brain as well as the carcass must be retained in cold storage until the test results are known.

The frequency of atypical cases is another unknown. Published (7,12) and unpublished (11,13) observations

indicate that in some countries it might be as high as 5%–10% of the total number of older animals diagnosed by rapid screening tests (e.g., 2/27 in Germany, and 1/9 in Canada), which would seem to be a surprisingly high proportion of spontaneously occurring cases. However, data are not yet sufficient to estimate the overall prevalence of atypical BSE, i.e., cases per million tested animals of all ages.

In this context, a word is in order about the US testing program. After the discovery of the first (imported) cow in 2003, the magnitude of testing was much increased, reaching a level of >400,000 tests in 2005 (Figure 4). Neither of the 2 more recently indigenously infected older animals, with ambiguous or no clinical features, would have been detected without such testing, and neither would have been identified as atypical without confirmatory Western blots. Despite these facts, surveillance has now been decimated to 40,000 annual tests (USDA news release no. 0255.06, July 20, 2006) and invites the accusation that the United

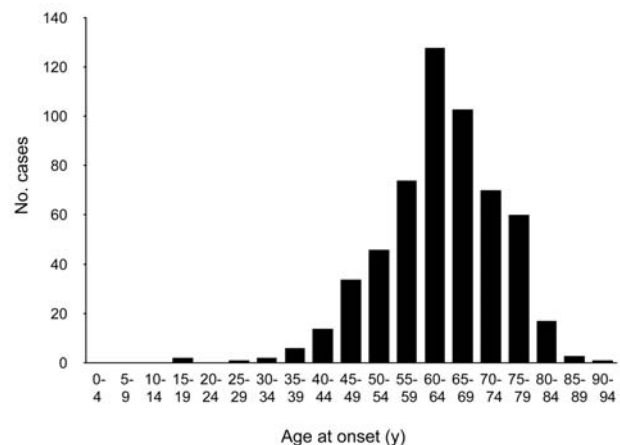


Figure 1. Distribution of ages at onset of illness in 500 cases of neuropathologically verified or experimentally transmitted sporadic Creutzfeldt-Jakob disease. Approximately 10% of cases occur in patients during the middle third (25–49 years) of a human lifespan, which corresponds to age in cattle of ~7–13 years.

Table 2. Summary of atypical cases of bovine spongiform encephalopathy (BSE)\*

Country	Age, y	Breed	Symptoms	Neuropathology		Western blot pattern
				Spongiform changes	Immunohistochemistry	
Italy	11	Bruna Alpina	None	Mild	Plaques	L
	15	Piemontese	None	Mild	Plaques	L
Denmark	14	Charolais	None	NR	NR	L
Poland	12	Black-white breed	None	Present	Positive (no plaques)	L
Japan	2	Holstein	None	Absent	Negative	L <sub>1</sub>
	14	Japanese Black	Dystasia	Severe	Positive (no plaques)	H
Belgium	5.5	East-Flemish	None	Absent	Negative	L <sub>1</sub>
France	10	Cross breed	None	NR	NR	H
	15	Prim Holstein	None	NR	NR	H
	8	Charolais	None	NR	NR	H
The Netherlands	13	Black-white Holstein, Freisian	NR	Present	No plaques	H
Sweden	12	Mixed Charolais	Recumbent	NR	Positive (no plaques)	H <sub>1</sub>
Switzerland	19	Zebu	Suspected	Typical BSE	Positive (no plaques)	H
Germany	13	Angus	NR	Absent	Positive (no plaques)	H
	15	Holstein-Freisian	NR	Absent	Positive (no plaques)	L
USA	12	Brahma cross	Falling	Absent	No plaques	H
	10	Red crossbred	Recumbent	Absent	No plaques	H
Canada	16	Charolais	Recumbent	NR	Positive (no plaques)	H

\*L, lower molecular weight; H, higher molecular weight (the 2 major Western blot PrP glycoproteins that distinguish the strains from each other and from the pattern seen in typical BSE); NR, not reported. Only the Italian cows and Swiss zebu had full neuropathologic examinations (others were limited to examination of the obex). Details are not available for additional animals with both H and L strains in France and Poland, and of the animal with H strain identified in Switzerland.

States will never know the true status of its involvement with BSE.

In short, a great deal of further work will need to be done before the phenotypic features and prevalence of atypical BSE are understood. More than a single strain may have been present from the beginning of the epidemic, but this possibility has been overlooked by virtue of the absence of widespread Western blot confirmatory testing of positive screening test results. These new phenotypes may be found, at least in part, to result from infections at an older age by a typical BSE agent, rather than neonatal infections with new "strains" of BSE. Neither alternative has yet been investigated.

### Sporadic CJD

The possibility that at least some cases of apparently sporadic CJD might be due to infection by sporadic cases of BSE cannot be dismissed outright. Screening programs needed to identify sporadic BSE have yet to be implemented, and we know from already extant testing programs that at least a proportion of infected animals have no symptoms and thus would never be identified in the absence of systematic testing. Thus, sporadic BSE (or for that matter, sporadic disease in any mammalian species) might be occurring on a regular basis at perhaps the same annual frequency as sporadic CJD in humans, that is, in the range of 1 case per million animals.

Whether humans might be more susceptible to atypical forms of BSE cannot be answered at this time. Experimentally transmitted BSE shows shorter incuba-

tion periods than BSE in at least 1 breed of cattle, bovinized transgenic mice, and *Cynomolgus* monkeys (12,13). In humanized transgenic mice, BSE transmitted, whereas typical BSE did not transmit (13). Paradoxically, the other major phenotype (H) showed an unusually long incubation period in bovinized transgenic mice (12).

The limited experimental evidence bearing on a possible relationship between BSE and sporadic CJD is difficult to interpret. The original atypical BSE strain of BSE had a molecular protein signature very similar to that of 1 subtype (type 2 M/V) of sporadic CJD in humans (5). In another study, a strain of typical BSE injected into humanized mice encoding valine at codon 129 showed a

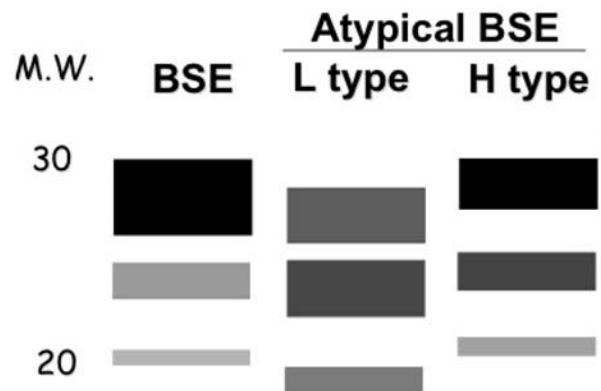


Figure 3. Representation of Western blots of PrP<sup>TSE</sup> patterns of typical bovine spongiform encephalopathy (BSE) and the 2 major types of atypical BSE. M.W., molecular weight in kilodaltons; L type, atypical "light" pattern; H type, atypical "heavy" pattern.

## PERSPECTIVE

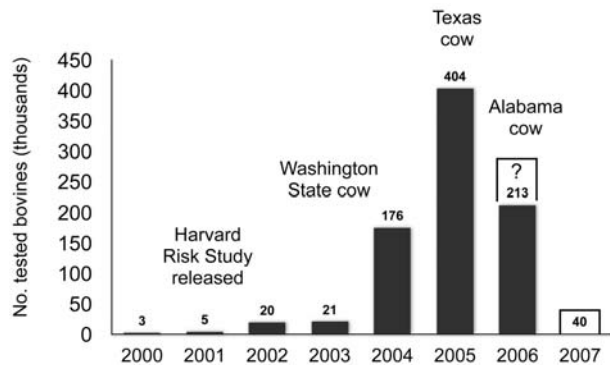


Figure 4. Numbers of tested cattle in the United States, 2000–2007. Number tested in 2006 as of October; number tested in 2007 proposed by the US Department of Agriculture.

glycopolymers indistinguishable from the same subtype of sporadic CJD (15). In a third study, the glycopatterns of both the H and L strains of atypical BSE evidently did not resemble any of the known sporadic CJD subtypes (12).

To these molecular biology observations can be added the epidemiologic data accumulated during the past 30 years. The hypothesis that at least some cases of apparently sporadic CJD are due to unrecognized BSE infections cannot be formally refuted, but if correct, we might expect by now to have some epidemiologic evidence linking BSE to at least 1 cluster of apparently sporadic cases of CJD. Although only a few clusters have been found (and still fewer published), every proposed cluster that has been investigated has failed to show any common exposure to bovines. For that matter, no common exposure has been shown to any environmental vehicles of infection, including the consumption of foodstuffs from bovine, ovine, and porcine sources, the 3 livestock species known to be susceptible to transmissible spongiform encephalopathies. Additional negative evidence comes from several large case-control studies in which no statistically significant dietary differences were observed between patients with sporadic CJD and controls (16,17).

On the other hand, the difficulty of establishing a link between BSE and CJD may be compounded by our ignorance of the infectious parameters of a sporadic form of BSE (e.g., host range, tissue distribution of infectivity, route of transmission, minimum infectious dose for humans, whether single or multiple). Presumably, these parameters would resemble those of variant CJD that is, high infectivity central nervous system and lymphoreticular tissues of an infected cow find their way into products consumed by humans. Transmissions that might have occurred in the past would be difficult to detect because meat products are generally not distributed in a way that results in detectable geographic clusters.

Barring the discovery of a specific molecular signature (as in variant CJD), the most convincing clue to an association will come from the observation of trends over time of the incidence of typical and atypical BSE and of sporadic and variant CJD. With 4 diseases, each of which could have increasing, unchanging, or decreasing trends, there could be 81 ( $3^4$ ) possible different combinations. However, it is highly likely that the trends for typical BSE and variant CJD will both decrease in parallel as feed bans continue to interrupt recycled contamination. The remaining combinations are thus reduced to 9 ( $3^2$ ), and some of them could be highly informative.

For example, if the incidence of atypical BSE declines in parallel with that of typical BSE, its candidacy as a sporadic form of disease would be eliminated (because sporadic disease would not be influenced by current measures to prevent oral infection). If, on the other hand, atypical BSE continues to occur as typical BSE disappears, this would be a strong indication that it is indeed sporadic, and if in addition at least 1 form of what is presently considered as sporadic CJD (such as the type 2 M/V subtype shown to have a Western blot signature like BASE) were to increase, this would suggest (although not prove) a causal relationship (Figure 5).

Recognition of the different forms of BSE and CJD depends upon continuing systematic testing for both bovines and humans, but bovine testing will be vulnerable

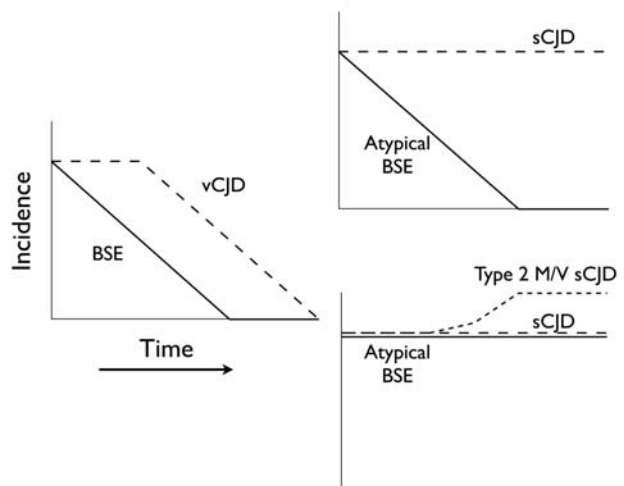


Figure 5. Diagram of 2 possible informative trends in the incidence of bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jakob disease (CJD). The left panel shows the likely trends of typical BSE and variant CJD (vCJD). The right upper panel shows 1 possible pair of trends of atypical BSE and sporadic CJD (sCJD) that might occur in conjunction with the typical BSE/vCJD trends, and would be consistent with the interpretation that atypical BSE is not sporadic and not related to sCJD. The right lower panel shows a second possible associated pair of trends consistent with the interpretation that atypical BSE is sporadic and might also be related to the type 2 M/V subset of apparently sCJD.

to heavy pressure from industry to dismantle the program as the commercial impact of declining BSE cases ceases to be an issue. Industry should be aware, however, of the implications of sporadic BSE. Its occurrence would necessitate the indefinite retention of all of the public health measures that exclude high-risk bovine tissues from the animal and human food chains, whereas its nonoccurrence would permit tissues that are now destroyed to be used as before, once orally acquired BSE has disappeared.

### Acknowledgments

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Dr Brown has recently retired after a 41-year career in the Laboratory of CNS Studies at the National Institutes of Health, where he focused on studying transmissible spongiform encephalopathies.

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