Stage 1:

MAD COWS OF KENT

Deborah E. Allen

It all began when a farmer in Kent, England, noticed his herd behaving rather strangely. His cows had begun walking with a peculiar gait, seemed to be in a constant state of apprehension, and were hypersensitive to sound and touch. A few of the animals became unmanageably aggressive (have you ever tried to milk a demented cow?).

This "mad cow disease" (as it came to be known in the popular press) began to spread all over England. Four years after the Kentish herd showed signs of the disease, the total number of reported cases had risen to 22,000.

The fact that no one knew how the disease was being spread was cause for initial concern among farmers, veterinarians, and officials and scientists at the agricultural ministry. When reports came in that the disease could jump to other species, including cats and laboratory mice that had been fed the minced brains of mad cows, public concern and anxiety reached epidemic proportions. Was eating hamburgers now a serious health hazard to the British public? Or, as *The Economist* queried in a banner headline, were cows now "Mad, Bad, and Dangerous to Eat"?

A clue to the mysterious origins of mad cow disease was actually deciphered back in 1986 when a neuropathologist examined specimens of brain tissue from the Kentish farmer's herd. He noticed that the tissue had an appearance similar to that of sheep infected with a condition known as scrapie (named after an interesting symptom—intense itching that prompts the sheep to rub themselves against fences or other handy scratching posts). It was spongy in appearance (so pockmarked with holes that it resembled Swiss cheese) and contained clusters of rod-like fibrils. Because of the resemblance between the infected cow and sheep brains, mad cow disease was given the formal scientific name of "bovine spongiform encephalopathy" (BSE).

Mad cow disease now had an official name, but its cause was still a mystery. Unlike a typical infectious disease of viral or bacterial origin, BSE did not invoke an immune response in its bovine victims; yet like infectious diseases, it could spread rapidly within an infected herd.

Questions to ponder:

- How do infectious diseases usually spread within and between herds of domesticated animals? What are the possible mechanisms? What modern agricultural practices help prevent their spread?
- After this first BSE scare, John Gummer, Britain's Minister of Agriculture, was photographed eating hamburgers with his 4-year-old daughter. Was this attempt to convince the British public that beef was safe to eat a good idea? What factors did you consider in forming this opinion?

Stage 2:

MAD COWS OF KENT

Stanley Prusiner, a neurologist at the University of California, San Francisco, came up with a controversial hypothesis for the origin of BSE, scrapie, and Gerstmann-Straussler-Sheinker syndrome (GSS), a spongiform encephalopathy that affects humans and runs in families. He postulated that these diseases are caused by prions (short for proteinaceous infectious particles), or abnormal, infectious proteins.

Some of the initial evidence for his hypothesis came from relatively simple observations. In the case of scrapie, for example, infected brain tissue in which the nucleic acids were destroyed by radiation or chemicals could still be used to infect lab mice. On the other hand, scrapie-infected tissue in which the proteins had been destroyed (using a combination of enzymes that break down proteins) was not infective. Finally, the brain tissue of animals with spongiform encephalopathy was found to have a protein (PrP) that is an abnormal variant of one normally kept in check by cellular enzymes. In spongiform encephalopathy, this aberrant form instead accumulates to form rod-like fibrils that resemble those found in infected brain tissue. In humans with GSS, Prusiner has found a mutation in the form of the gene producing the normal version of the protein. Some scientists began to speculate that this aberrant form of the protein was actually the prion itself.

Prusiner's critics asked, however, how a protein (with no nucleic acid associated with it) could enter a cell and make enough copies of itself to create a disease in its host. They bolstered their first round of attacks on Prusiner's hypothesis by pointing out that when this abnormal cellular protein is cloned and injected into test animals, they do not become infected.

Questions to ponder:

- Is it possible that prions could still be the culprits, despite the fact that the cloned protein mentioned in the scenario above wasn't infectious?
- How could a prion cause an infectious disease? Suggest a possible mechanism.
- Athough Dr. Stanley Prusiner was awarded the Nobel Prize in Medicine in 1997 for his work on prions, his discoveries are still regarded with skepticism by some researchers, and he is often referred to as a "maverick" scientist. Is this reluctance to accept new and controversial ideas a routine part of the process of science, or is this (Prusiner and prions) a special case?

Stage 3:

MAD COWS OF KENT

In 1996, the British government finally released a statement admitting that consumption of beef from mad cows was the most likely explanation for the recent appearance in England of a previously unknown form of human dementia. Christened "new variant Creutzfeldt-Jacob disease (vCJD)", it had by then contributed to the deaths of 14 (unusually young) individuals in the United Kingdom (*Nature* 385:197, 1997), whose brains upon autopsy had the characteristic spongiform degeneration and some more unusual neuropathologic features. These new cases more closely resembled the cow disease than they did the usual cases of Creutzfeldt-Jacob.

Meanwhile, back in the U.S.A., a 1996 popular press report (*Newsweek* 127[15]:58, 1996) stated that according to the USDA, 14 percent of cattle carcasses rendered each year were fed to other U.S. cattle. It has also been standard practice in this country to add rendered sheep tissue to cattle feed. This practice has since been banned by an FDA regulation that went into effect in June 1997. A U.S. embargo on the importation of all cattle and cattle products originating in Great Britain has been in place since 1989, despite the fact that Britain has discontinued many of the practices thought to have been responsible for the mad cow disease outbreaks since 1988. No case of mad cow disease has yet been detected in the United States, but the annual incidence of scrapie in sheep remains about 30 to 50 cases per 8 million animals.

Questions to ponder:

- Now that these bans are in place in the United States, is it likely that mad cow disease will be a problem in this country? In your opinion, are there additional protective measures that need to be taken?
- Are you convinced that prions are the most likely transmissible agent of BSE and other transmissible spongiform encephalopathies? Why or why not?

Topics Introduced by the Problem:

MAD COWS OF KENT

Basic Background Topics

(Your textbook can be consulted for information on these.)

- Infectious processes in diseases of microbial and viral origin
- Immune system responses to viruses and bacteria
- Prions
- The structure and function of proteins
- How proteins are modified after they are made
- The normal structure and function of brain cells

More Advanced Topics

(You may need to consult additional resources for information on these.)

- Koch's postulates
- The epidemiology of BSE (and prion diseases of humans and sheep)
- Molecular biology of prions
- Husbandry of herd animals that humans consume
- FDA regulations concerning animal feed (animals for human consumption)
- Pathological changes associated with prion diseases

Additional Resources for Researching Problem Content:
MAD COWS OF KENT

Articles and books:

Caldwell, M. 1991. "Mad Cows and Wild Proteins." *Discover* April:69–74. (This account of the first major BSE outbreak was the principal source used to write the first version of this problem in 1993.)

Gibbs, C. J., Jr., editor. 1996. ***Bovine Spongiform Encephalopathy: The BSE Dilemma***. New York: Springer.

Kolata, G. 1997. "Scientists Split over Prion Hypothesis." *New York Times* October 7:18.

Prusiner, S. B. 1996. "The Prion Diseases." ***Scientific American*** 272:48–55. (Also online at <http://www.sciam.com/0896issue/prion.html>.)

Rhodes, R. 1997. ***Deadly Feasts***. New York: Simon and Schuster.

United States Congress, House Committee on Government Reform and Oversight. 1997. ***Potential Transmission of Spongiform Encephalopathies to Humans: The Food and Drug Administration's (FDA) Ruminant to Ruminant Feed Ban and the Safety of Other Products: Hearing Before the Committee on Government Reform and Oversight, House of Representatives, One Hundred Fifth Congress, First Session, January 29, 1997***. Washington, D.C.: U.S. Government Printing Office.

Additional Resources for Researching Problem Content:
MAD COWS OF KENT

Electronic resources:

Baumbach, G. Department of Pathology, University of Iowa College of Medicine. "Infectious Diseases of the Central Nervous System Parenchymal Infections: Prions." ***The Virtual Hospital.*** <http://vh.radiology.uiowa.edu/Providers/TeachingFiles/CNSInfDisR2/Text/ PInf.CDE.html>

Brown, J. C. Department of Microbiology, University of Kansas. ***What the Heck Is "Mad Cow" Disease?*** <http://falcon.cc.ukans.edu/%7Ejbrown/madcow.html>

Brewer, S., J. Novakofski, and R. Wallace. University of Illinois at Urbana Champaign. ***BSE—Bovine Spongiform Encephalopathy ("Mad Cow Disease").*** <http://w3.aces.uiuc.edu/AnSci/BSE/>

FDA Center for Veterinary Medicine. ***BSE Documents.*** <http://www.cvm.fda.gov/fda/TOCs/bsetoc.html>

Thomasson, W. A. "Unraveling the Mystery of Protein Folding." ***Breakthroughs in Science—FASEB.*** <http://www.faseb.org/opar/protfold/protein.html>

University of Wisconsin. "Mad Cows: Behind the British Beef Scare." ***The Why Files: Science Behind the News.*** <http://whyfiles.news.wisc.edu/012mad_cow/>

World Health Organization. "Bovine Spongiform Encephalopathy (BSE) Fact Sheet (N113 March 1996)." ***Emerging and Other Communicable Diseases (EMC).*** <http://www.who.ch/programmes/emc/bsefacts.htm>