

IN FOCUS

DEADLY ENIGMA

The U.S. wakes up to
the threat of mad cow disease
and its relatives

It is, in the words of one group of researchers, "a true quandary." How can an abnormal form of a protein present in all mammals cause some 15 different lethal brain diseases that affect animals as diverse as hamsters, sheep, cattle, cats and humans? Yet the dominant theory about the group of illnesses that includes scrapie in sheep, mad cow disease in cattle and Creutzfeldt-Jakob disease in humans holds just that. What is certain is that some mysterious agent that resists standard chemical disinfection as well as high temperatures can transmit these diseases between individuals and, less often, between species. What is unknown is how the agent spreads under natural conditions and how it destroys brain tissue. Because of the characteristic spongelike appearance of brain tissue from stricken animals, the diseases are called transmissible spongiform encephalopathies (TSEs).

Finding the answers is a matter of urgency. In Britain, mad cow disease, or bovine spongiform encephalopathy, has turned into a national calamity. A worldwide ban is on British beef and livestock imports. The government is slaughtering all cattle older than 30 months--some 30,000 a week--to allay fears that the disease, which causes animals to become nervous and develop an unsteady gait, will spread to people. So far British medical researchers have identified 14 unusual cases of Creutzfeldt-Jakob disease in young people that they suspect were a human manifestation of mad cow disease. New studies of the victims' brains appear to strengthen that conclusion. The biochemical properties of the suspected disease-causing protein in the brains of the victims are distinctly different from those usually found in Creutzfeldt-Jakob disease, supporting the notion that the disease came from a novel source.

Apprehensive that the U.S. cattle industry could be in line for a disaster like the one in Britain, in October the Food and Drug Administration was about to propose controls on the use of animal-derived protein and bone meal in cattle feed. Mad cow disease is believed to have spread in Britain because of the practice of incorporating material from the rendered carcasses of cattle and other animals into cattle feed. That cannibalistic practice is also standard in the U.S.

Although only one case of the disease has been confirmed in North America--in an animal imported from Britain to Canada--other TSEs, including scrapie in sheep and comparable diseases in mink and mule deer, are well known in the U.S. Nobody has any idea whether some native scrapielike agent could transform itself into mad cow disease or something unpleasantly like it. "As long as we continue to feed cows to cows we are at risk," says Richard F. Marsh of the University of Wisconsin, who has studied TSE in mink. The cattle-rendering industry, however, is resisting blanket bans and wants to see controls only on tissues for which there is firm evidence of infectivity.

Unfortunately, the science of TSEs generally is not in a firm state. Laboratory tests show that the diseases have variable and strange characteristics. They are most easily transmitted by injecting brain tissue from an infected animal into a recipient's brain, but sometimes eating brain or other offal will do the job. (Kuru, a human TSE formerly common in Papua New Guinea, was spread because the Fore people ritually consumed the brains of their dead.) There are distinct strains of some TSEs, including scrapie and Creutzfeldt-Jakob disease, but passage through a different species can permanently alter the diseases' pathological characteristics in the original host species.

The leading theory that ties these characteristics together comes from Stanley B. Prusiner of the University of California at San Francisco [see "The Prion Diseases," by Stanley B. Prusiner; Scientific American, January 1995]. The theory posits that a ubiquitous mammalian protein called prion protein can, rarely, refold itself into a toxic form that then speeds the conversion of more healthy protein in a runaway process. Some mutant forms of the protein are more likely to convert spontaneously than others, which accounts for rare sporadic cases. TSEs are thus both inherited and transmissible, and unlike those of any other known diseases, the pathogen lacks DNA or RNA.

Some of the strongest evidence for Prusiner's theory is his demonstration that mice genetically engineered to produce an abnormal prion protein develop a spongiform disease and can transmit illness to other mice via their brain tissue. Critics, such as Richard Rubenstein of the New York Institute for Basic Research, note that the mice in these experiments contain very little of the abnormal prion protein that is supposed to be the disease agent. So, Rubenstein argues, they may not be truly comparable to animals with TSEs. Perhaps, Rubenstein and others suggest, some toxin in the brains of the sick experimental mice caused the recipients of their tissue to become sick, too. Prusiner maintains,

however, that no ordinary toxin is potent and slow enough to give his results.

Prusiner insists his most recent experiments, which employ elaborate tests designed to rule out possible sources of error, make his theory unassailable. And one of Prusiner's chief rivals, Byron W. Caughey of the Rocky Mountain Laboratories of the National Institutes of Health in Hamilton, Mont., has made the protein-only theory more plausible by experiments that he believes replicate the process by which TSEs propagate in the brain. Caughey and his associates have shown that under specific chemical conditions, they can convert some of the normal prion protein into the abnormal form in the test tube. Moreover, abnormal proteins from different strains of scrapie, which are chemically distinguishable, seem to produce their own strain-specific type of abnormal protein.

Caughey believes his experiments indicate that normal, healthy prion protein changes into the pathological variant when it forms aggregates of some 20 to 50 molecules. The process gets under way if it is seeded by a piece of the abnormal aggregate. Together with Peter T. Lansbury of the Massachusetts Institute of Technology, Caughey has proposed a geometric model illustrating that aggregates can form in different crystalline patterns corresponding to different TSEs.

Caughey says he is keeping an open mind on whether there might be some DNA or RNA along with the protein that might help explain the variety of TSEs. The ultimate proof of the protein-only theory would be to fabricate abnormal protein from simple chemicals and show that it caused transmissible disease in animals, but neither Caughey nor anyone else can do that. Caughey's experiments still need a seed from a sick animal, and the amount of abnormal protein the experiments produce is not enough to prove that the freshly created material can cause disease.

Prusiner, for his part, is not about to concede to Caughey. He believes aggregates are merely an artifact of Caughey's experimental procedures. "There are no ordered aggregates of polymers of prion protein in cells in the brain," he declares. Prusiner's studies lead him to think, instead, that an as yet unidentified "protein X" is responsible for converting the normal prion protein to the scrapie form. He and his co-workers have synthesized fragments of the healthy prion protein and shown that they can spontaneously form fibrils that resemble those seen in the TSE diseases.

Whether protein-only prions can explain TSEs or not, it will take

more than a decade for British scientists to unravel how BSE spreads, predicts D. Carleton Gajdusek of the NIH, who first showed how kuru spreads. A test for TSEs in humans and in a few animals was announced in September, but so far it seems to perform well only when clear symptoms of illness have already developed. Although the test may be useful to confirm suspected TSEs in humans, the most important step for governments to take, Gajdusek says, is to maintain intensive surveillance for patients with unusual neurological symptoms. His pictures and descriptions of children with kuru have been distributed to neurologists in Europe to help them recognize possible victims.

--Tim Beardsley in Washington, D.C.
