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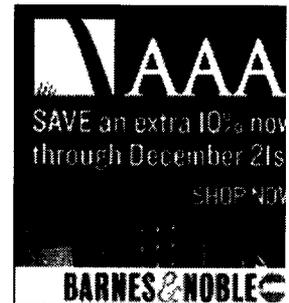
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NEWS FOCUS

SPONGIFORM DISEASES: After the Crisis: More Questions About Prions

Martin Enserink



With "mad cow disease" declining sharply, public anxiety about prion diseases has diminished. But cutting funds would be a big mistake, prion researchers say

DÜSSELDORF, GERMANY--Peering over an audience of more than 700 researchers on 19 October, Nobel laureate Stanley Prusiner seemed pleased. "This is probably the largest gathering of prion scientists ever," boasted the field's controversial godfather, who gave the keynote speech at a recent meeting. "As the crowd attested, prion science had come along way since Prusiner proposed a heretical idea 23 years ago that it is not viruses or bacteria, but weird proteins, that cause a family of lethal brain diseases.

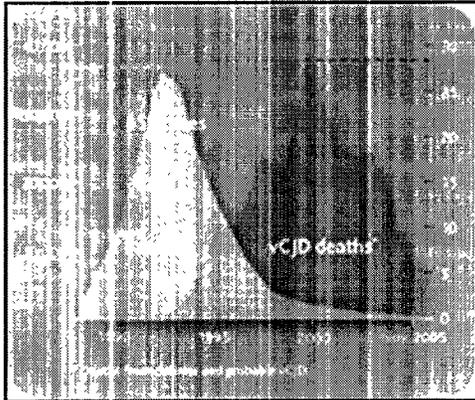
But now, leaner times may be ahead. Public health efforts to combat prion infections in cattle have worked so well that reports about "mad cow disease" have all but vanished from the newspapers; the clamor for action is fading, and governments are looking for ways to scale back costly safety measures. And many worry that research may suffer; trimming has begun in Germany and France. Prusiner captured the atmosphere best in a private quip after his keynote speech, according to conference organizer Detlev Riesner of Heinrich Heine University, when he said the largest prion meeting to date could end up being the largest in history.

Prion researchers admit there's reason to breathe a little easier. Outbreaks of mad cow disease, or bovine spongiform encephalopathy (BSE), have declined ever since reaching a peak in the United Kingdom, by far the hardest-hit nation, in 1992. Fears of a massive wave of an associated human brain disease called variant Creutzfeldt-Jakob disease (vCJD) have not materialized.

But a slowdown in research would be the wrong response, prion scientists say. The British vCJD outbreak could still be in its infancy, and medical procedures could trigger a second wave. (Tests to screen blood, organs, and tissue are still some time away.) There are other reasons to stay alert as well. Europeans have reported the appearance of a new form of scrapie, an age-old prion disease in sheep. And a prion disease in North American deer and elk is spreading rapidly. "The fire is out, but there are still glowing red spots everywhere," says Jean-Philippe Deslys, head of the prion research group at the French Atomic Energy Commission.

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Twin peaks. Both mad cow disease (BSE) and human variant CJD cases have declined sharply in Britain. But some experts warn that vCJD could bounce back.

CREDIT: SOURCES: OIE (BSE); NATIONAL CJD SURVEILLANCE UNIT (vCJD)

And leaving aside public and animal health, researchers say their field has barely begun to crack its mysteries.

Debatable

Even after decades of research, the most fundamental question about the prion family of diseases remains open: What is the infectious agent? Many researchers today say recent experiments have convinced them that Prusiner's dogma-defying theory is correct: A rogue protein imposes its own misfolded shape on other, healthy proteins--but some still have doubts (see sidebar on p.1758).

And other riddles remain. For example: After oral infection, how do prions travel from the gut to the brain? They are known to pass through lymphoid tissue and peripheral nerves, but do individual misfolded proteins make that journey, or do they infect their neighbors, causing them to fall like dominoes? Once present in the brain, misfolded proteins form aggregates that appear to be involved in killing neurons. But exactly how is unclear.

Fortunately, answers to these questions weren't needed to start bringing the BSE and vCJD epidemics under control. Primarily as a result of a 1988 ban on feeding so-called rendered protein, including brain tissue, from ruminants to ruminants, the number of BSE cases in the United Kingdom began to fall in 1993; there were only 343 last year and just 151 so far in 2005 (see graphic). Other countries in Europe, after discovering about the year 2000 that they had their own BSE problems, now report rapid declines, too.

In reaction, the European Union (E.U.) is beginning to loosen measures to stop BSE and limit human exposure. A "road map" for prion diseases, published by the European Commission in July, listed restrictions that might eventually be lifted, arguing that resources should be concentrated on new health threats such as avian influenza. (Testing of apparently healthy animals at the slaughterhouse cost about 1.6 billion between 2001 and 2004-- 1.6 million per BSE case detected.)

And in October, the commission delighted lovers of T-bone steak and other meat on the bone by raising the age from 12 to 24 months at which the vertebral column--one place where prions concentrate--is removed. (Generally produced from cattle aged 22 to 30 months, such cuts had virtually disappeared.) That decision was premature, says Martin Groschup of the Friedrich Loeffler Institute, Germany's federal animal health center. His lab is still carrying out a long-term BSE pathology study to discover at what age and where in the cow's body infectious particles collect; the decision should have been stayed pending the outcome, he says.

Thanks in part to the decline of BSE, more scientists are now turning their attention to sheep. Scrapie has been known to infect flocks for at least 250 years and is harmless to humans. But in the lab, sheep can also be infected with BSE. Researchers have long worried that the resulting disease--simply called "BSE in sheep"--could get into Europe's flocks, for instance, through feed. If it were transmissible among sheep, like scrapie, it would pose a special problem because a feed ban would not get rid of it, says Lucien van Keulen of the Central Institute for Animal Disease Control in Lelystad, the Netherlands.



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But so far, there's no evidence of this.

The increased surveillance has turned up a new problem, however. In the last 3 years, researchers in Germany, Portugal, and France have discovered a new variety of scrapie whose prion proteins accumulate in different parts of the brain, have different biochemical properties, and produce a slightly different set of symptoms. Most likely, says Groschup, it's a variant of scrapie that flew under the radar until now. What's disconcerting is that it also appears to affect sheep with a genotype called ARR/ARR, thought to confer resistance to scrapie. Now, some worry that an ambitious E.U. breeding program aimed at spreading that genotype could just replace classical scrapie with a new form. "It's another thing we need to get to the bottom of," says Neil Cashman of the University of British Columbia in Vancouver, Canada.

Meanwhile, in the United States and Canada, chronic wasting disease (CWD), first discovered in deer and elk in Colorado and Wyoming in the 1980s, keeps turning up in new places. In 2005, New York became the 13th state affected, and moose the fourth species. So far, there is no evidence that CWD can cross the species barrier to humans--nor, for that matter, nonmembers of the deer family. CWD hasn't appeared in Europe, but the E.U. is planning a survey in 2006 to make sure.

Deceptive calm?

In BSE's wake, vCJD is declining too; there were just nine deaths last year in the United Kingdom, down from 28 in 2000 (see graph), and the total death toll stands at 153 (plus fewer than 20 in other countries), far below worst-case predictions in the late 1990s.



Old news. Concern about vCJD cases made headlines in the 1990s. Now that the crisis seems to be over, some public health and

research measures are being scaled back.

CREDIT: TOUHIG SION/CORBIS

But some believe the curve may be deceptive. John Collinge of the National Hospital for Neurology and Neurosurgery in London notes that vCJD's peak came barely 10 years after the highest BSE exposure in Britain. The delay is just too short, he says. Kuru, a disease among the Fore people in the highlands of New Guinea that resulted from cannibalistic rituals in the 1950s, has a mean incubation period of about 12 years. BSE ought to take longer, Collinge says, because in all known instances, crossing a species barrier lengthens a prion disease's incubation period.

Collinge suggests another possibility: Only the most genetically susceptible people have developed symptoms so far. Researchers know that having the "wrong" amino acid at codon 129 of both copies of the prion gene makes a person more susceptible to vCJD. All patients so far except one, who likely contracted vCJD through a blood transfusion, had this genotype, called MM. But other genes may be involved as well, says Collinge; the victims so far may just be an especially susceptible vanguard of the MM population at large, which comprises 40% of U.K. residents.

The possibility that many more people harbor the disease without symptoms--and the fact that probable vCJD transmission through blood transfusions has now been shown twice--means that, rather than slacking off now, efforts to develop drugs and diagnostic techniques should be intensified, Riesner says. At the meeting, several groups reported encouraging data that could lead to a blood test within the next several years. Drug development has been slower, in part because the pharmaceutical industry has little interest in a disease that affects about one in a million people.

Researchers have tried at least half a dozen compounds on CJD patients, but most seem to prolong life by only a few weeks--if they do anything. An ongoing U.K. trial of a drug called quinacrine for vCJD and CJD, in which 53 patients have been enrolled, is primarily a way to discover how to run future tests, says Collinge, whose group is one of three massscreening small compounds in vitro in a search for promising new candidates.

Because of the countless remaining questions, many scientists say they worry about the unmistakable decline in public interest. Cashman, for instance, says he was amazed a "media firestorm" didn't break out after a paper in the October issue of *Nature Medicine* showed that prions can lurk in the inflamed mammary glands of scrapie-infected sheep--and presumably their milk as well. If the same is true in cows, he said, "it would be a hugely important finding for public health."

So far, funding doesn't appear under threat in the United States or the United Kingdom, and it is even expanding in Canada. Three weeks ago, the Canadian government announced a new U.S. \$30 million network of centers of excellence; separately, the government of the province of Alberta has committed \$33 million to launch a prion research institute. The reason: Canada recently learned how devastating prion diseases be. Four cases of BSE since 2003 have cost the economy an estimated \$5.5 billion. (As Cashman puts it, "those cattle might as well have been space shuttles--they cost the same.")

But in Germany, prion projects worth about 10 million, funded by three federal ministries since 2001, will come to an end in 2006; they include the German Transmissible Spongiform Encephalopathy Research Platform, which coordinates studies and sample sharing through three depositories. Several German states' programs will end next year as well, says Kerstin Dressel, the platform's scientific secretary. In France, funding is set to decline as well, Deslys says.

Still, not everyone is worried. If it turns out that after BSE, prion diseases pose no major new health risks, well, "then it would only be natural that the money goes elsewhere," says Byron Caughey, a veteran prion researcher at the U.S. National Institute of Allergy and Infectious Diseases Rocky Mountain Laboratories in Hamilton, Montana. "Then we'll have to adapt, as scientists do."

* Prion 2005. [Between Fundamentals and Society's Needs](#). Düsseldorf, 19-21 October.