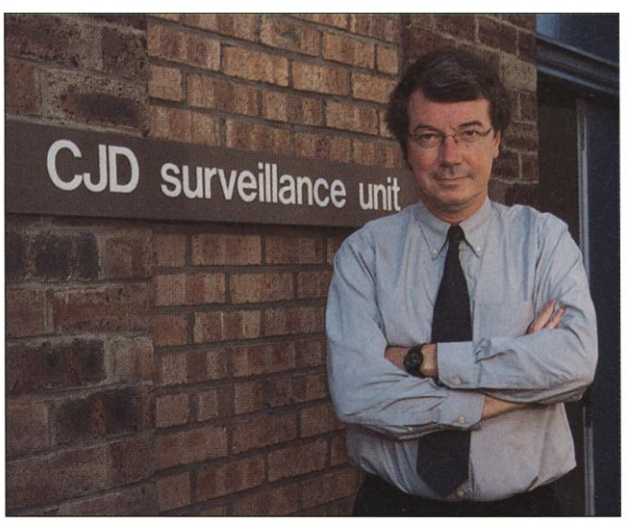
An Edinburgh task force studies cases of variant Creutzfeldt-Jakob disease, trying to find out just how the patients got infected and how many of them there may ultimately be

Tracking the Human Fallout From 'Mad Cow Disease'

EDINBURGH, SCOTLAND—When neurologist Andrea Lowman is called in on a case, the news is seldom good. The patient she had come to see earlier this summer was no exception. A young woman in her early 20s had been admitted to a hospital in England after her speech became increasingly slurred and she began having difficulty walking. By the time Lowman examined her, she was almost totally incoherent, her body jerked with involuntary movements, and she was suffering from ataxia, a loss of motor coordination.

After looking over the young woman's medical charts and talking with her parents—who were keeping a sorrowful vigil by their daughter's bedside—Lowman confirmed the preliminary diagnosis the woman's own physician had arrived at: Creutzfeldt-Jakob disease (CJD), an incurable malady of the brain and nervous system. Moreover, because of the patient's youth and the pattern of her symptoms, Lowman suspected that she was suffering from a new form of the affliction—called variant CJD (vCJD)—which has been linked to eating beef or other products from cattle infected with bovine spongiform encephalopathy (BSE), or "mad cow disease."



Prion vigilante. Neurologist Robert Will and his team track every case of CJD in the United Kingdom.

Two or three times each week, Lowman travels from her office at the National CJD Surveillance Unit in Edinburgh to visit another suspected victim of CJD. U.K. health authorities created the unit in May 1990 in the wake of the BSE epidemic, which erupted in the mid-1980s and affected thousands of cattle each year for more than a decade. BSE had been linked to an abnormal, apparently infectious protein called a prion, which may have entered the bovine food chain when ground-up carcasses of prion-infected sheep were included in animal feed. And despite the insistence at the time by agricultural officials and farm industry organizations that British beef was safe, health experts were worried that the disease might spread to humans—a nightmarish possibility that came true in 1996 when the surveillance unit reported the first cases of vCJD.

In the years since, the unit has continued to study the vCJD epidemic closely, looking for clues about exactly how the disease was transmitted to humans. On her travels across the United Kingdom, for example, Lowman is accompanied by a research nurse, who asks the patients' families detailed questions about what their relatives ate, down to the brand of baby food they consumed. This job has only increased in importance as the death toll continues to climb. During the past few weeks, the team's work has been making new headlines. In the 5 August issue of *The Lancet*, the researchers, along with other U.K. collaborators, reported for the first time that it is seeing a real increase in vCJD incidence, amounting to a 23% annual rise between 1994 and the present.

The number of confirmed or probable vCJD cases in the United Kingdom is still relatively small—a total of 80 as *Science* went to press—but "this is the first time we have had good statistical evidence of an upward trend," says neurologist Robert Will, the surveillance unit's director. Where that upward trend will ultimately lead is, however, highly uncertain. A new estimate by epidemiologist Roy Anderson's team at Oxford University, published in the 10 August issue of *Nature*, now puts the maximum number at 136,000, far less than their previous estimate of 500,000—and, the authors note, the actual toll could turn out to be much lower.

Equally unclear is the exact source of those infections. Although most scientists believe that human consumption of BSE-contaminated meat products is the most likely explanation for the rise of vCJD, they are still unsure about which products were responsible. Some researchers are now hoping that an unusual "cluster" of five vCJD cases centered on the Leicestershire County town of Queniborough, which is currently under intense scrutiny by epidemiologists, will provide some answers. Knowing what kinds of food products were infected "might be important for correctly modeling the epidemic and knowing how many cases to expect," says Philip Monk, the county's public health consultant.

Watching and waiting

When the Edinburgh team, which is funded by the U.K. Department of Health and Scotland's Executive Health Department, was formed, there were as yet no signs that BSE had infected humans. But health experts had good reason to be concerned. They already knew that BSE-infected cattle had been slaughtered for food—indeed, some 750,000 infected animals eventually entered the human food chain. And research during the previous decade had strongly implicated prions in some human neurodegenerative diseases such as kuru, a CJD-like disease discovered in the Fore people of New Guinea and thought to be transmitted directly or indirectly through cannibalism.

The government asked Will, one of the United Kingdom's leading experts on CJD, to head the new unit. He recruited James Ironside, a highly respected neuropathologist, to join him, and together with a small team of staff and consultants the pair set about monitoring every case of CJD or CJD-like symptoms in the country. "The

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aim was to look at the incidence and pathological features of CJD in the U.K.," says Ironside. "We wanted to see if anything was changing that might be attributable to BSE. But at that stage we had no idea of what we might be looking for—an increase in typical cases, a different type of disease, or nothing at all."

For 5 long years the team watched and waited, logging in more than 200 cases of CJD. But every case turned out to be a previously recognized variety of the disease. Most were the so-called "sporadic" form, which has no known cause and usually appears in older patients. Then, in late 1995, the vigilance paid off. From the nationwide network of neurologists and pathologists Will and Ironside had organized, they learned that two teenagers had been diagnosed with CJD, followed soon afterward by a case of CJD in a 29-year-old patient.

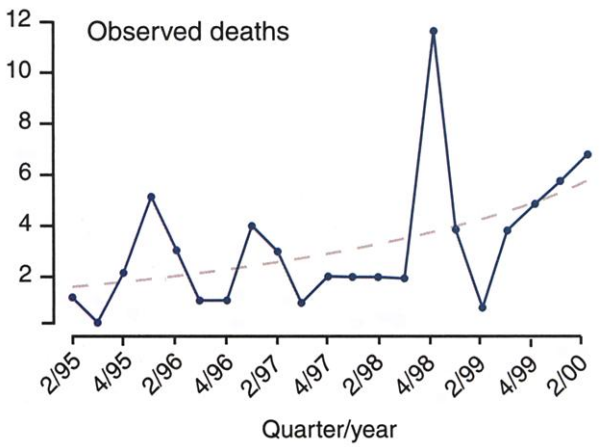
These cases were striking for a number of reasons. The patients were unusually young. They showed an atypical clinical pattern, including psychiatric symptoms and ataxia very early in the course of the disease. And microscopic examination of their brain tissue revealed that it was studded with clumped deposits of prion protein, called "florid plaques," reminiscent of those seen in kuru and very distinct from the more diffuse pattern of brain damage usually seen in sporadic CJD.

By 6 April 1996, when the surveillance unit and its collaborators published this bad news in *The Lancet*, 10 cases of vCJD had been identified. The onset of a new disease hard on the heels of the BSE epidemic, and at that time restricted to the United Kingdom (although there are now several vCJD cases in France), led the researchers to conclude that infection with BSE was "the most plausible interpretation" of the findings. This view soon received considerable support when researchers at the Institute for Animal Health in Edinburgh reported that the prion strain apparently responsible for vCJD was nearly identical to that identified in cattle infected with BSE.

Sticking to the data

The news that humans had likely been infected with BSE hit the United Kingdom like a bombshell. It led to the near-bankruptcy of the British cattle industry and was a key factor in the defeat of the Conservative government, which had generally downplayed the danger from BSE, by the Labor Party in the 1997 parliamentary election. With the media frenzy and occasional public panic swirling around them, Will and his team have painstakingly collected the data needed to shed light on how the epidemic got started and where it may be going. Simon Cousens, a statistician at the London School of Hygiene and Tropical Medicine who collaborates closely with the surveillance unit, describes the team as constantly walking a tightrope between "scare mongering and creating panic, or being accused of covering things up."

The team has consistently shied away from making predictions about the future course of the epidemic, preferring to stick to the data it already has in hand and taking care not to exaggerate the numbers. So far, says Will, "there are more farmers who have committed suicide because of vCJD than people who have actually been victims of the disease." The study reported last month in *The Lancet*, which concludes that the incidence is going up, is based on a statistical reanalysis of existing data, using the date of onset of disease rather than date of death to define when the case occurred. Because some patients live longer than others after diagnosis, this provides a more sensitive indicator of vCJD incidence, says surveillance unit epidemiologist Hester Ward. As for making projections of the eventual case toll, Ward says, "I don't think we will be able to tell the size of the epidemic until we've reached the peak and started coming down."



On the rise. A new analysis shows that the vCJD incidence and death rate are going up steadily. (The dotted line is the fitted underlying trend calculated from the actual data points.)

Those researchers bold enough to make projections, such as Anderson's Oxford team, have had to continually adjust their figures. The researchers, who had earlier predicted by mathematical modeling a maximum toll of 500,000 cases, have now capped their estimate at 136,000 over the coming several decades—while emphasizing that the real numbers will probably be much lower.

In making their predictions, the team assumes that the slaughtering of infected herds and other safeguards have put a stop to new human infections with the BSE prion. And the maximum estimate of 136,000, says Oxford mathematical biologist Neil Ferguson, is based on another assumption: that the incubation period for vCJD—that is, the time between initial prion infection and the development of symptoms—is 60 years or more. But this, he adds, is highly unlikely. "We can't say what the incubation period really is, but it is unheard of that a disease has an incubation period that long," Ferguson says. A more realistic maximum is likely to be about 10,000 cases.

Yet, although the number of potential cases might be lower than once feared, researchers remain determined to try to solve the riddles posed by vCJD. In particular, they want to know why the disease occurs almost entirely in younger people—the average age of the victims identified so far is some 30 years less than that for sporadic CJD—and what food products might have transmitted it. So far, the only clue is the finding that vCJD incidence in the northern half of the United Kingdom is about twice that in the south. "We have no explanation for this," says Ward. However, the team is considering a number of hypotheses, including the possibility that northerners eat more "mechanically recovered meat," a major ingredient in products such as hot-dogs and sausages—and a suspected source of BSE infection because it contains much more nervous-system tissue than would be found in a nicely trimmed steak.

New hope of getting an answer has been raised by a cluster of five vCJD cases diagnosed over the past few years in people living either in the town of Queniborough or within a 5-kilometer radius of it. Such clusters are the meat and potatoes of epidemiological work, because they provide researchers with the opportunity to identify risk factors common to all the cases. A previous suspected cluster, in Kent County, evaporated when it turned out to be due only to chance. But the cluster in Queniborough—a town of only 3000 people—seems different. "The probability of getting that many cases so close together in that size population by chance is extremely small, about 1 in 500," says Cousens. "These cases are linked in some way."

Even so, identifying the source of these infections may be difficult. Although the families of the victims have been given the surveillance unit's standard questionnaire, Will says that "trying to get dietary habits secondhand from relatives is notoriously un-

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reliable. There is a potential for bias in the study. Everyone knows the hypothesis we are testing"—that meat or meat products were responsible. Nevertheless, Monk told *Science*, he has developed his own hypothesis about the source of infection in the town, which he declines to state publicly at this point to avoid bias in the study. Monk is now testing his hypothesis by asking every parent in Queniborough with children aged 19 to 35 to fill out a new questionnaire about what they fed their offspring between 1975 and 1990, the period during which most exposure to BSE is likely to have taken place. "I am confident that we will find the link between these cases," he says.

Will says that although this knowledge would come too late to help victims of vCJD, it could be important to their families, many of whom are worried that the brothers and sisters of their stricken children might have eaten the same products and thus also face a risk of dying from the disease. And this information might help Lowman comfort the distraught family members she sees each week, by convincing them that they could not possibly have known that the food they gave their offspring was infected. "The parents often feel very guilty," Lowman says. "They are terribly upset that they might have exposed their own children to something that made them ill."

–MICHAEL BALTER

TEACHER TRAINING

How to Produce Better Math and Science Teachers

In two new reports on improving science and math education in the United States, National Research Council panels call on universities and school districts to share responsibility for educating teachers and suggest that new Ph.D.s are an untapped source for high school teachers.

Schools, Universities Told to Forge Links

Universities train most of the nation's science and math teachers. But it's the job of local school districts to ensure that they keep up with their field once they enter the classroom. That bifurcated system needs to be ended, says a new report* from the National Research Council (NRC), if the country hopes to improve student performance in math and science. That message is likely to be repeated next month, sources say, when a high-profile commission issues its recommendations on how to improve the quality of the nation's math and science teachers—and puts a price tag on the reforms.

"Universities have to attract students to their education departments, but after they graduate and find jobs as teachers they are no longer a client of the university," says panel member Mark Saul, a teacher at Bronxville High School outside New York City and an adjunct professor of mathematics at City College of New York. "And school administrators have to deal with so many noneducational crises that they're happy if the kids are in their seats and there's a licensed teacher in each room. As a result, attention to the actual act of instruction gets lost."

The NRC panel says that the best way to improve teacher education is to make it a continuum, with school districts taking more responsibility for the initial preparation of new teachers and university faculty playing a bigger role in ongoing professional development. The change will require both sectors to work together more closely. It also recommends that universities improve the content of undergraduate science and math courses for prospective teachers, model appropriate practices for teaching those subjects, and do more research on the art of teaching and how students learn. In turn, school districts should make better use of teachers who have mastered these skills, giving them more opportunities to share their knowledge with their colleagues and with student teachers.

Reeducation. Teachers need a continuum of training, says a new report, to keep abreast of latest pedagogy and new knowledge.

Such a partnership already exists in Maryland, notes panelist Martin Johnson, a professor of mathematics education at the University of Maryland, College Park, in the form of four Professional Development Schools (PDSs). PDSs bring together prospective teachers and experienced staff in a formal arrangement that goes beyond both regular student teaching and standard after-school workshops. "In the past, we would send students to a school and they'd be assigned to one teacher," says Johnson. "We're asking the school to incorporate the student teacher into a broader range of experiences, with input from other faculty members as well as other teachers."

Jim Lewis, head of the math department at the University of Nebraska, Lincoln, and co-chair of the NRC committee, compares this approach to training doctors. "Medical students take courses from both research and clinical faculty," he explains, "and their residencies are overseen by practicing physicians. Likewise, an experienced classroom teacher may be a better mentor [to a prospective teacher] than an education professor who focuses on research." That shift, says Lewis, will allow research faculty to devote more attention to helping experienced teachers stay on top of their field through advanced courses, summer research projects, and other professional activities.

The National Science Foundation, which paid $425,000 for the report and two related activities, has already begun to support the types of partnerships the NRC panel calls for. It has asked for $20 million next year to expand a program on university-based Centers for Learning and Teaching with teacher training as one of three primary foci.

The NRC report also dovetails with the pending recommendations of a blue-ribbon federal commission headed by former U.S. senator and astronaut John Glenn. "I was struck by the amount of overlap," says Linda Rosen, executive secretary to the commission, whose report is due out on 3 October (www.ed.gov/americacounts/glenn/toc.html). "There's a growing sense that we have to break down the barriers between elementary

CREDIT: PROJECT 2061

* Educating Teachers of Science, Mathematics, and Technology: New Practices for the New Millennium, 2000 (national-academies.org).