MAD COW DISEASE

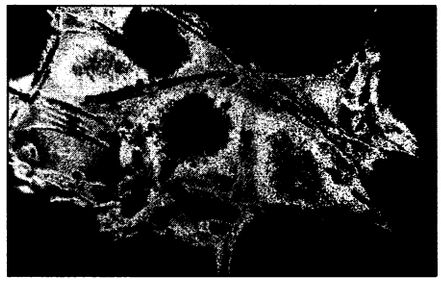
Scant Data Cause Widespread Concern

CAMBRIDGE, U.K.—Perhaps there was no way the British government could have avoided setting off a public panic last week, when it announced that 10 cases of a fatal human neurodegenerative disorder called Creutzfeldt-Jakob disease (CJD) may be linked to a similar disorder that has felled thousands of head of cattle in Britain. The government's press release contained scant detail of the scientific data behind the announcement—which are not yet published—but emphasizes that no link has been proven. To many of the British public, however, who had heard 10 years of official assurances, the news represented an abrupt about-face: "Can We Still Trust Them?" ran next morning's headline in the 21 March *Daily Express*.

The announcement, a five-page statement from the Ministry of Health, was based on the conclusions of an independent committee of scientists, known as the Spongiform Encephalopathy Advisory Committee. The committee examined 10 cases of CJD, diagnosed in Britain over the past 7 months, which involve several unusual but consistent features, the most striking being the young age of those afflicted. "The most likely explanation" for these infections, the committee concluded, was exposure to bovine spongiform encephalopathy (BSE), the disorder popularly known in Britain as "mad cow disease." While these cases do not provide direct evidence of a link, they are "cause for great concern," the committee stated.

The concern stems from research carried out by the government-funded CJD Surveillance Unit at the Western General Hospital in Edinburgh, the results of which are expected to be published in *The Lancet* within a few weeks. The unit was established in 1990 when an outbreak of BSE was at its height in Britain. The disease is believed to have been transmitted to cows in the early 1980s through feed that contained the remains of sheep infected with scrapie, another related neurodegenerative disease, and there were fears that it might cause CJD in humans who ate beef from infected animals. BSE has already spread into other species, such as mice, cats, and some zoo animals—presumably also via contaminated feedstuffs—and in laboratory experiments mice can be infected with BSE by injection of certain proteins from infected bovine brains. But until now there has been no sign that it has spread to humans.

Neuropathologist James Ironside of the CJD Unit says the 10 cases that are now raising concern—out of 40 or so cases of CJD reported in Britain in the past year—suggest that a new variant of CJD has arisen. "Firstly, they're in younger individuals," Ironside told *Science*, with an average age of 29, compared with age 63 for all CJD cases. They were first diagnosed because of psychiatric disorders, such as anxiety and depression, followed by movement disorders, he says; older patients first experience dementia. In addition, CJD typically causes a characteristic pattern of electrical activity in the brain, but this was absent in the 10 cases. Finally, says Ironside,



EM UNIT/CVL/PHOTO RESEARCHERS

Mad cow brain. Brain tissue from cow with BSE shows fibrils and spongy lesions.

pathology." The patients' brains showed a very widespread distribution of clumps of protein, called plaques. These do crop up in a classical CJD brain, but in nowhere near such densities. "There seems to be far more of the protein," says Ironside.

Some of the individuals affected were known to be keen consumers of beef burgers; another had regularly visited a relative's dairy farm. The scientists excluded other possible medical and genetic causes for the new variant of CJD, leaving open the possibility that it was triggered by ingestion of BSE-infected meat. They are, however, a long way from determining exactly how the 10 cases arose.

About 15% of all CJD cases are inherited, and geneticists have tracked down a specific gene that is mutated in such families, called *PRNP*. The genetic mutations can also occur sporadically, for unknown reasons. The gene codes for a "prion" protein, which is believed to be an infectious agent when in its mutant form. (Some researchers believe an additional, unknown element or virus is also required to effect transmission.) The normal form is a glycoprotein on the surface of neurons throughout the central nervous system.

Fred Cohen, a pharmacologist and biophysicist at the University of California, San Francisco, says that even if the BSE prion protein is responsible for the 10 anomalous cases of CJD, "I think what we're looking at is an extremely rare event." But "take 50 million people over 10 years," and the number of events is increased, Cohen says, referring to the population of the United Kingdom and the decade since BSE first appeared in British beef herds. Researchers and public alike await details of these, and perhaps more, cases.

–Claire O'Brien

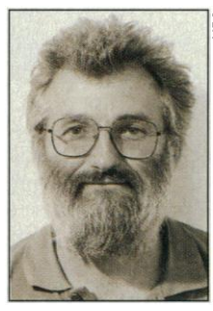
Claire O'Brien is a writer in Cambridge, U.K.

HUMAN GENOME PROJECT

Sequencers Split Over Data Release

HEIDELBERG, GERMANY—By the end of the session on sequencing at last week's Human Genome Organization (HUGO) meeting here, few attendees were unaware that the era of whole-genome sequencing has arrived—and with it some tough issues for the research community. After talks on the huge scale-up in sequencing capacity at two large genome centers, André Goffeau of the Catholic University of Louvain in Belgium announced that a multinational team has finished sequencing all 12 million bases of the baker's yeast genome, making it the first eukaryotic genome to be completely sequenced. The achievement drew a long round of spontaneous applause from a standing-room-only audience. But the reaction was less enthusiastic when Goffeau went on to say that the final portion of the sequence (up to 20%) would not be made public until 30 April.

Goffeau defended the delay on the grounds that the scientists who did the work deserve to be the first to reap some benefits. "We cannot just give this away," he said—a view shared by a few researchers, especially those from small labs, who spoke with *Science* later. But the practice contrasts strikingly with the immediate-release policies of the two sequencing powerhouses, Washington University in St. Louis and the Sanger Centre near Cambridge, U.K. And the issue of data release is so worrisome to some researchers that it occupied much of the agenda at a recent meeting in Bermuda, where scientists and funders involved in large-scale sequencing tried to hammer out principles aimed at increasing openness—such as releasing data quickly and refraining from applying for patents on raw sequence data with no known function. "There is lots of tension in the community over these issues," says genome researcher Michael Ashburner of the University of Cambridge and the European Bioinformatics Institute.



MRC

Supports openness. John Sulston.

The issue is coming to a head

as centers in the United States, Europe, and Japan gear up to sequence the 3 billion bases of the human genome. Already, the Sanger Centre and the Washington University group led by Robert Waterston together churn out nearly a million bases of new sequence weekly (mostly from the nematode *Caenorhabditis elegans*), and they plan to increase two- to three-fold within a year. Both centers release preliminary sequences every day, rather than waiting until they are polished to finished quality or first combing the data to pick out choice bits for themselves. And the research community has responded eagerly, with several thousand queries monthly on these data.

The yeast sequencing project, funded largely by the European Union (EU), took a different tack by involving five main centers plus dozens of mostly small European labs, many of which started out with little sequencing experience. The MIPS database group at the Max Planck Institute for Biochemistry in Martinsried, Germany, checked, assembled, and annotated the data, and participating scientists had time to analyze it. Although some researchers chose to release their sequences, the remaining data often stayed hidden for months.

That created bad feeling. "The community is very frustrated by this arbitrary withholding of data," says yeast researcher Hugh Pelham of the U.K. Medical Research Council's Laboratory of Molecular Biology in Cambridge. Nonparticipating scientists can send test sequences to MIPS, where it is searched against the confidential data. But if there is a "hit" the sender is not given the matching sequence but the name of the person who sequenced it, with whom they can try to strike a deal. "It is like waving a red rag in front of a bull," says Pelham. "I simply do not understand the EU's stand."

It was against this background of radically different practices that Britain's Wellcome Trust—the medical charity that funds the Sanger Centre—convened the Bermuda gathering in late February. Scientists from sequencing centers in the United States, Europe, and Japan, plus representatives from their funding agencies, met to discuss how to coordinate who does what and to develop guiding principles for public funders of large-scale sequencing projects. Barbara Skene, manager of Wellcome's genetics program, says participants unanimously agreed that fast data release is desirable and that patenting raw sequence is not. But they also recognized that such policies may be difficult to implement.

Coordinating the sequencing itself is turning out to be the easy part. "Sequencing is so expensive that ... everyone is eager to avoid duplication of effort," says Sanger Centre Director John Sulston. The Bermuda group came up with the idea that centers declare on the World Wide Web what they intend to sequence. If there are overlaps, the groups involved should simply work it out—for example, by sharing the sequencing of that chromosomal region.

The data release and patent issues are far trickier. The U.S. National Institutes of Health, which funds most of the country's Human Genome Project, cannot legally restrict researchers or their institutions from applying for patents, says Elke Jordan, deputy director of the U.S. genome office. "We are very supportive of these sentiments. ... But we can only urge applicants [to comply]," she says. In Germany, where a sequencing program is expected to be announced soon, potential industrial backers may not agree to release data without a waiting period, while in Japan, sequence data must be checked by the Science and Technology Agency before release.

It is also unclear what effect these policies would have on patenting sequences, says Joseph Straus of the Max Planck Institute for Foreign and International Patent, Copyright, and Competition Law in Munich, who chairs HUGO's committee on intellectual property rights. In Europe, unlike the United States, information already made public cannot be patented, he says. And he is concerned that third parties could scan each day's new data for something patentable with only a minimum of extra information. "If the idea is to prevent or hamper unnecessary patents, you may not get the effect you're seeking," he says.

All this suggests that agreeing on these issues may be a long, tough process. "What we want to do is to encourage openness [and] start urging funding agencies toward a consensus," says Skene, who is drafting a "statement of principles" based on the Bermuda meeting. The Bermuda statement, she hopes, will be an important step in building that consensus.

–Patricia Kahn

EARTHQUAKE PREDICTION

Chair Quits Japan Panel in Protest

TOKYO—The head of a committee of Japanese seismologists responsible for telling the government when unusual seismic phenomena mean a large-scale earthquake is about to strike a region near Tokyo has resigned after failing to win the right to say "maybe." Kiyoo Mogi, professor emeritus of the University of Tokyo's Earthquake Research Institute, has spent the past 5 years arguing for the authority to issue a "warning" that would stop short of a firm prediction. "But Japan's bureaucrats just won't accept change" in the current yes/no policy, he says. "We would think it very funny if weather forecasters could only give the chance of rain as being 0% or 100%, and earthquake forecasting is much more difficult."

Koichi Uhira, deputy director of earthquake prediction information for the Japan Meteorological Agency, which manages the prediction program, says the agency needs more information to decide whether such a third option is appropriate. "We repeatedly asked Professor Mogi for specifics on when observed data would justify such a warning," says Uhira, "but we never got an explanation."

The prediction program, the most elaborate in the world, is intended to anticipate a magnitude-8 earthquake thought to be overdue for the Tokai region, a densely populated area about 150 kilometers west of Tokyo. Meteorological Agency technicians monitor data around the clock from more than 150 instruments measuring seismic activity, rock strain, crustal tilt, and tide and ground-water levels. Mogi's Earthquake Assessment Committee is convened if anomalous phenomena are detected. If the committee decides that an earthquake is imminent, the prime minister is required to issue a declaration that would close stores and schools, reroute traffic, and put emergency services on alert. The committee has never met on such an emergency basis in its 17-year history, much less reached a decision, and the prime minister has never ordered an alert.

A charter member of the six-person assessment committee and its chair since 1991, Mogi believes it is possible in some cases to make an accurate prediction. But he is troubled that a decision with such large economic consequences may have to be made in the face of scientific uncertainty. For this reason, he proposed the option of issuing an earthquake warning, which would result in slowing—but not stopping—traffic and taking other halfway measures. Another panel member, Katsuyuki Abe, professor of seismology at the Earthquake Research Institute, supports the idea and says the final call should be left to politicians, not scientists. If the panel's analysis of anomalous phenomena falls into a gray area, Abe says, "it should be up to the director of the Meteorological Agency to decide whether it is black or white."

Although the government spends more than $100 million a year on the prediction program and associated prediction research, the effort enjoys only spotty support from scientists in Japan. The public is also leery about the chances of predicting any earthquakes (*Science*, 16 February, p. 910). Despite that skepticism, there is no sign other committee members will follow Mogi's lead and resign. Uhira says the agency has no plans to change the prediction program and expects to appoint a new chair shortly.

–Dennis Normile