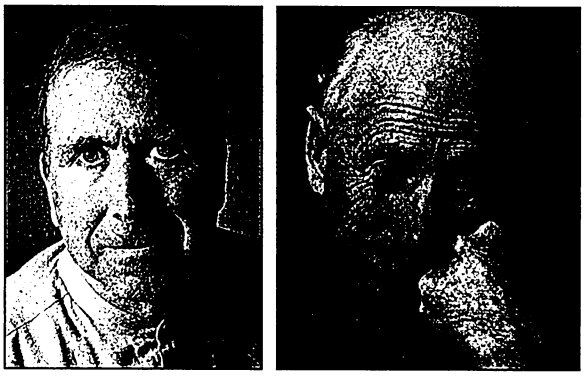
quire legions of taxonomists and parataxonomists as well as massive but user-friendly computer databases. And those legions would have to be concentrated in the most biodiverse parts of the world—the developing countries—where both trained naturalists and computer access are scarce. The foundation hosted a meeting in Mexico City earlier this fall to underscore its desire to involve developing-country scientists. But good intentions have failed before—such as in Costa Rica. And developing nations are concerned that Western countries might take advantage of their biodiversity for profit's sake (*Science*, 9 May 1997, p. 893).



Whole-species catalog. High-tech gurus Kevin Kelly and Stewart Brand are behind the push for a total species count in 25 years.

And then, of course, there's the money. Whether the odd combination of high-tech gurus and academic taxonomists can ratchet a modest foundation into a multibillion-dollar international effort remains to be seen. Kelly hopes to raise $10 million by the end of 2002, mainly in large chunks from foundations and wealthy individuals. Phelan adds that the goal is to raise $50 million to $100 million in the next 3 years. "If we can deploy $3 million next year, we could kick-start things and get some traction," she says.

Ultimately, the scale of the effort will require national and international funding. In the United States, at least, that may be hard to find: Biologists are still smarting from congressional rejection of the proposed National Biological Survey. Lawmakers feared a species inventory could ultimately infringe on the rights of owners of private property. But Raven, who moderated a session at the Harvard meeting, says that Kelly's foundation is an encouraging step. "The All [Species Foundation] effort is a publicity gold mine, if played right," he says.

Many of the taxonomists at the Harvard meeting scoffed at the idea that an all-species count could be done in 25 years. But whether or not the California high-techies can pull it off, senior researchers welcome the nascent foundation and its infusion of funds. "People are spread out, underappreciated, and consider themselves fly or beetle or butterfly people rather than taxonomists," says Scott Miller, entomology department chair of the Smithsonian's National Museum of Natural History. The big-list idea and help from Silicon Valley might prove just the tonic needed to give purpose, direction, and unity to a tradition-bound field.

–ANDREW LAWLER

INFECTIOUS DISEASES

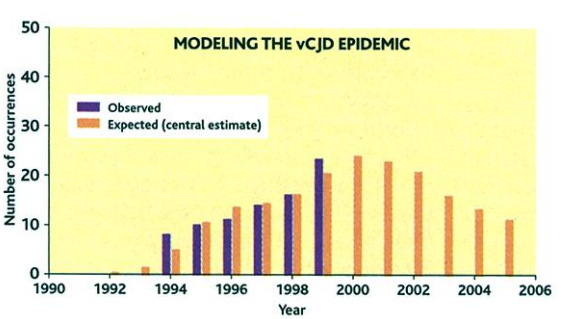
Uncertainties Plague Projections of vCJD Toll

Two mathematical models of the epidemic come up with very different results. Researchers may soon know if one is right

Since 1996, when a new human disease linked to eating beef from cattle infected with bovine spongiform encephalopathy (BSE)—"mad cow disease"—first emerged, the British public has been gripped by one question: How bad will the epidemic be? By late September 2001, 107 people living in the United Kingdom had died from variant Creutzfeldt-Jakob disease (vCJD), an invariably fatal neurodegenerative malady. But just how many more it might claim remains unclear.

Although an estimated 750,000 BSE-infected cattle were eaten by humans between about 1980 and 1996, no one knows how many people actually became infected, nor how long it takes for an infected person to become sick. Past projections of the possible death toll have not relieved the uncertainty. The most authoritative estimate to date predicts that cases could range from a few hundred to more than 100,000. The waters became even murkier last week when a study concluding that sheep might also have been infected with BSE—a possibility health officials have long feared—was pulled from publication at the last minute when it turned out that the scientists might have been analyzing brains of cattle rather than sheep (see sidebar).

In the midst of this confusion, two well-respected teams have been refining their projections—and they are coming up with different conclusions. A new mathematical analysis of the epidemic by researchers at the London School of Hygiene and Tropical Medicine provides some encouraging news. The study, published online by *Science* on 25 October (www.sciencexpress.org), concludes that the epidemic might be nearing its peak and that the maximum number of cases might number no more than "several thousand." The team, led by epidemiologist Peter Smith, believes that the real numbers could turn out to be much lower than that. Moreover, says veterinary epidemiologist Mark Woolhouse of the University of Edinburgh in Scotland, the new study's more optimistic predictions might be "very testable in the short term." But these hopes are challenged by epidemiologist Roy Anderson's group at Imperial College in London. This group's newly completed but still unpublished analysis, which uses different mathematical techniques, comes up with maximum estimates that are "substantially higher," says team member Neil Ferguson.



Good news? If one mathematical projection is correct, the number of human cases may soon peak.

The fact that different mathematical models produce different results is not surprising, researchers say. Because reliable tests for BSE infection in humans do not yet exist, it is impossible to know how many people were actually infected and when. Without such data, modelers must rely on "arbitrary mathematical assumptions to guide the extrapolations," says epidemiologist Peter Bacchetti of the University of California, San Francisco.

Until now, the most oft-cited projections were those reported by Anderson's team in the 10 August 2000 issue of *Nature*. Anderson and his colleagues explored more than 5 million combinations of parameters based on a wide range of assumptions, including the likelihood that an infection would result from eating

CREDITS: (TOP) (KELLY) MICHAEL SEXTON; (BRAND) TOM GRAVES

Is BSE in Sheep a No-Brainer?

Efforts to mathematically model the epidemic of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom are fraught with unknowns (see main text). But all bets would be off if it turned out that humans got the disease not only from mad cows but also from mad sheep. This possibility, which has given health officials nightmares in recent years, could eventually help fuel an explosion of vCJD cases (*Science*, 17 March 2000, p. 1906).

Last week, officials thought this bad news was about to break. An Edinburgh-based team from the U.K.'s Institute for Animal Health (IAH) was on the verge of publishing, in the online edition of the *Journal of General Virology*, experiments indicating that samples of sheep brain might be harboring bovine spongiform encephalopathy (BSE), or "mad cow disease." But the paper was pulled at the last minute when the institute, doing a last check on the source of the samples, was told by an independent laboratory that the material it thought was sheep brain actually came from cattle. The IAH is now conducting an internal audit to see if this is indeed the case, and if so, how it could have made such a mistake.

Mad or not? A lab mix-up leaves uncertain whether sheep harbor BSE.

The episode has left the public reputation of the IAH—which has made some of the most important discoveries in this field—in tatters. "BSE Tests Conducted on Wrong Brains," cried a headline in the London *Times*. But epidemiologist Peter Smith, chair of the government's Spongiform Encephalopathy Advisory Committee, says it "would be wise to withhold judgment" about what really happened. Smith adds that the affair provides "no reassurance" that sheep don't harbor BSE. Chris Bostock, IAH's chief, says that early this year the government's Veterinary Laboratories Agency (VLA)—which had previously done its own analysis of the samples—had reassured him that they appeared to be 100% sheep. But when a second lab concluded last week that it was all cattle brain, the team decided to withdraw the paper. Shortly afterward, Bostock says, the VLA contacted him to say its laboratory had analyzed the wrong samples and was now withdrawing its original reassurance that they were pure sheep.

Bostock complains that the British press has pronounced the IAH guilty of making a mistake before all the proof is in. "If there is an error on our part, we will state that," he says. Until then, Bostock insists, there should be no rush to judgment: "We have to balance this with a decade of high-quality work in this field."

–M.B.

BSE-laden cattle and the effectiveness of government attempts to control the spread of BSE. They came up with a maximum of 136,000 cases over the next several decades.

The London School team used a very different approach, called "back-calculation," which Bacchetti and other researchers had already employed successfully to estimate the course of the HIV/AIDS epidemic. This technique calculates backward from current case numbers to recreate the original conditions that gave rise to the epidemic. It focuses on a much smaller number of assumptions, including guesses about how many people were infected by BSE, when they were infected, and the length of the incubation period. In all, the team used only seven variable parameters.

No matter how those seven parameters are varied, the upper limit of cases is "less than 10,000," says London School statistical epidemiologist Simon Cousens, a co-author of the paper. For example, even if many millions of people have been infected with BSE, the small number of cases to date suggests that the average incubation time is so long that "most of those people will die of other causes before they develop clinical disease," Cousens says. Conversely, if only a small number of people have been infected, the current case toll indicates that the average incubation time is fairly short.

Current vCJD case trends may lend some support to that conclusion, says Bacchetti. Although cases have been increasing about 20% to 25% annually over the past several years, the overall numbers are still quite small. Bacchetti says that the London School team's optimistic projections are "reasonable," because "we now have many years with no sign of ... explosive growth."

But the Anderson team believes that the London School's figures paint too rosy a picture. Ferguson suspects that the group's lower numbers are due to "the methodological approximations employed and differences in key assumptions." The most important reason for the difference, he says, is that the London School relied too heavily on reported cases of BSE in cattle before 1988, when health officials made reporting mandatory: "There is likely to have been really substantial underreporting of BSE cases in the early stages of the epidemic." Cousens counters that even if much higher BSE rates were assumed, it would not change his group's overall results: The London School's projections came out lower even when it was assumed that up to 12,000,000 members of the British public had been infected by BSE-laden cattle.

Both models may be too optimistic, the two teams agree, if one of the key assumptions they both made turns out to be wrong: that all victims of vCJD will share the same genetic profile. One thing that most vCJD researchers do agree on is that wayward proteins called prions, aberrant versions of the normal cellular protein PrP, are responsible in whole or in part for vCJD, BSE, and a host of other neurodegenerative diseases in humans and animals. So far, all the people diagnosed with vCJD have shared one characteristic: Their *PrP* genes, which come in two copies, code for two copies of the amino acid methionine at position 129 in the corresponding PrP protein. These methionine homozygotes, as they are called, exist in 40% of the British population. But several studies of another human prion disease, kuru, have shown that although methionine homozygotes have shorter incubation times, other genotypes are also susceptible. If the entire British public were susceptible, rather than just 40%, note the London School researchers, their worst-case estimates might have to be multiplied by a factor of 2.5.

Another factor that could boost worst-case numbers, some scientists say, is if other genetic factors—including those unrelated to the PrP gene itself—also affect long-term susceptibility. Such uncertainties "undermine these kinds of predictions," says neurologist John Collinge of St. Mary's Hospital in London, a longtime critic of attempts to mathematically model the epidemic.

Nevertheless, the London School researchers believe that if the fairly modest rise in new vCJD cases over the past few years does not dramatically increase, time may be on the side of their more optimistic projections. And because their study predicts that vCJD cases might reach a peak in the next few years, its accuracy should soon be clear. Says Woolhouse: "We will soon know if they are right."

–MICHAEL BALTER

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