Killer Flu with a Human-Pig Pedigree?
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Source: *Science*, New Series, Vol. 292, No. 5519 (May 11, 2001), p. 1041
Published by: American Association for the Advancement of Science
Stable URL: http://www.jstor.org/stable/3083618
Accessed: 15-09-2015 20:53 UTC

Institute, who has asked her to serve on many panels. Collins adds: "She will be a great champion for science and for women in science." Princeton graduate and genome researcher Eric Lander of the Massachusetts Institute of Technology in Cambridge describes Tilghman as a "great scientist, a true humanist, and a wonderful person," as well as "a spectacular choice for Princeton."

Tilghman was on the search committee until 6 weeks ago, according to the chair of the trustees' executive committee and head of the search committee, Robert H. Rawson Jr. She left a meeting early to teach, and in her absence, the other members decided they wanted her to become a candidate. She agreed and withdrew from the search committee. The remaining members chose her unanimously.

Tilghman—like Shapiro—was born in Canada. She joined Princeton's faculty in 1986, became a Howard Hughes Medical Institute investigator in 1988, and was elected to the National Academy of Sciences and the Institute of Medicine less than a decade later. She received Princeton's top teaching award in 1996. Since its founding in 1998, she has run Princeton's Lewis-Sigler Institute for Integrative Genomics; no successor has yet been named. **–ELIOT MARSHALL**

THE 1918 PANDEMIC

Killer Flu With a Human-Pig Pedigree?

LONDON—Scientists have come up with a new explanation for what made the Spanish flu the biggest killer of the 20th century. The deadly influenza did not jump from birds into humans, they argue, but rather was the unfortunate result of an unprecedented recombination of pig and human flu genes. "This is a great step away from the existing theories of the origin of 1918 flu," says virologist Mark Gibbs of the Australian National University in Canberra, whose team presented its findings at a symposium here on 25 April at the Royal Society.

Reassuringly, such genetic recombination appears to be an exceedingly rare event, suggesting that the odds of a reprise of the Spanish flu pandemic—which killed 40 million people around the world in 1918 and 1919—are vanishingly low. Some experts, however, argue that this proposed explanation for the Spanish flu's virulence is flawed: Recombination among flu strains, they assert, does not happen at all.

Four years ago in *Science*, a team led by virologist Jeffery Taubenberger of the Armed Forces Institute of Pathology in Washington, D.C., published the initial RNA sequences of the 1918 flu strain after isolating it from the preserved tissue of victims (21 March 1997, p. 1793). Poring over these data, Gibbs's team homed in on the gene for hemagglutinin (HA), a viral protein used to gain entry into target cells. Novel HA configurations are harder for the immune system to recognize, making the protein a key determinant of a strain's virulence.

The researchers used standard software to compare the sequence of the 1918 HA gene to those from 30 closely related influenza strains from birds, pigs, and humans. "Within a few hours we had a preliminary signal," says Gibbs. Pursing this further, they discovered that the 1918 version appeared to be a chimera of sorts: One end bore a marked resemblance to human flu sequences, the middle was strikingly similar to pig, while the other end again was human. The "simplest scenario," says Gibbs, is that the HA gene (which, researchers concur, originated in bird flu strains) slipped into mammals sometime before 1918 and diverged into two lineages, human and pig.

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Spanish flu victims. New work suggests that the 1918 strain derived its lethal powers from an unprecedented genetic recombination.

Then in a bad twist of fate, these HA genes recombined to form the version that made the Spanish flu so much harder for the immune system to recognize—and therefore more virulent. "It looks for all the world like the signature of recombination, and I can't see how to explain it otherwise," says Eddie Holmes, who studies viral evolution at the University of Oxford. "We are talking about a rare event, but evolution is all about rare events."

The idea has met with skepticism from some top flu researchers, however. Taubenberger, for one, argues that the Gibbs group has misinterpreted the 1918 sequence. He believes that an influenza virus with an avian HA gene had started circulating in humans just before the start of the pandemic. In the fall of 1918, this virus infected humans and swine simultaneously and split into two lineages, and disparity in the rate of evolution between the two strains since then has confused the picture, says Taubenberger. "Human flu viruses are subject to huge immunological pressure and are forced to mutate rapidly," as humans are so long-lived and develop immunity to many strains, he says, while pig strains mutate slowly because their hosts don't live long enough to develop such broad immunity. Thus, Taubenberger argues, the HA gene in the 1918 human samples resembled that of the avian ancestor of both pig and human strains. But by the 1930s—the date of the earliest strains that can be directly compared—the human gene had changed dramatically, while the pig gene had changed little. That, he says, would explain why sections of the 1918 human virus look similar to those of later pig viruses.

Taubenberger does not believe that flu strains—like other negative strand RNA viruses—are capable of recombination, in which new genes are patched together from sections of other genes. Not that flu strains are limited to evolution through mutation: A kind of whole-gene swapping between strains, called reassortment, is thought to have spawned the virulent avian flu strains that jumped into mammals in 1957 and 1968.

Gibbs acknowledges that it will be an uphill battle to convince some of his colleagues that influenza strains are capable of recombining. "One of the paradigms," he says, "is that flu goes in for reassortment but not for recombination." But, he argues, recombination provides the best explanation for the genetic data. **–JOHN PICKRELL**

U.S. SCIENCE POLICY

Former Advisers Fret Over OSTP Vacancy

CAMBRIDGE, MASSACHUSETTS—Although billed as a celebration, the largest gathering of U.S. presidential science advisers had more the air of a wake. Meeting here last week, the former government officials were all too aware that a new Administration is busy making critical decisions without benefit of the kind of scientific advice that has guided most presidents in the past half-century. "Nobody is celebrating the future here," says Neal Lane, former science adviser to President Bill Clinton and now a professor at Houston's Rice University.

Lane was one of eight former science advisers who gathered on 1 May at the Massachusetts Institute of Technology (MIT) to celebrate the 25th anniversary of the Office of Science and Technology Policy (OSTP).