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VIROLOGY

Resurrected Influenza Virus Yields Secrets of Deadly 1918 Pandemic

As worries about a new flu pandemic mount, researchers have figured out the traits that made the 1918 influenza virus, which killed between 20 million and 50 million people, so virulent. Although a study on page 77 sheds new light on these questions, it raises a host of others because the researchers reconstructed the complete virus, which no longer existed anywhere on Earth.

The team resurrected the 1918 pandemic virus by using gene sequences fished from preserved tissue from a 1918 victim. The virus is as lethal as expected, killing mice more quickly than any other human flu virus known. Recreating the 1918 strain "had to be done, and it's produced some extremely interesting results," comments flu researcher Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee.

Although a scientific triumph, the experiment has stirred debate over safety procedures for handling such a deadly virus. Moreover, a new federal biosecurity board gave the paper an unusual last-minute review to make sure the merits of its publication outweighed the risks of releasing potentially dangerous knowledge. The board's green light is a relief to scientists who have worried about a clampdown on scientific information following the anthrax attacks 4 years ago. "The system is working," suggests Massachusetts Institute of Technology molecular biologist Phillip Sharp, who wrote an accompanying editorial (p. 17).

The team, from the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, the Armed Forces Institute of Pathology (AFIP) in Washington, D.C., Mount Sinai School of Medicine in New York City, and the U.S. Department of Agriculture, says its work will provide crucial knowledge for heading off the next influenza pandemic, which could be brewing in Asia, where the H5N1 bird flu has killed more than 60 people. "This work has to be seen in a positive light," says lead author Terrence Tumpey of CDC.

The research grows out of AFIP pathologist Jeffrey Taubenberger's efforts, begun in 1995, to sequence the genome of the 1918 flu virus. Working mainly with tissue from a victim found in permafrost in Alaska, he and others have been piecing together the virus's eight genes and characterizing their protein products.

Last year, this work revealed the structure of the 1918 hemagglutinin (HA), the crucial surface protein that flu viruses use to latch onto host cells (*Science*, 19 March 2004, p. 1866); in a separate study, Yoshihiro Kawaoka's group at the University of Wisconsin, Madison, showed that a virus containing this HA was unusually potent. This week in *Nature*, Taubenberger's group publishes the sequences of the last three genes, which together encode the virus's polymerase, the machinery for virus replication.

With those final sequences in hand, Peter Palese's team at Mount Sinai then stitched the eight 1918 genes into a regular flu virus genome contained within bacterial DNA. They shipped these inert plasmids to Tumpey at CDC, who inserted them into cells to make live virus.

In this issue of *Science*, Tumpey, Taubenberger, and collaborators report how the reconstructed 1918 virus behaves. In experiments at CDC, the virus killed mice in 3 to 5 days and caused severe lung inflammation reminiscent of that reported by doctors who examined 1918 flu victims. The team also studied viruses with various combinations of 1918 genes and regular flu genes, which showed that "without that HA, the virus was not virulent," says Tumpey.

The 1918 flu had a couple of other tricks up its sleeve as well. One is that the virus doesn't need to rely on its host cells for the protease trypsin to cleave and activate the HA protein; instead, another surface protein, neuraminidase (NA), appears to help cleave the HA. That suggests the 1918 virus, like some highly virulent bird flu strains, can grow in any cell type, not just trypsin-laden lung cells. In addition, the 1918 flu's polymerase genes appear to allow it to replicate very efficiently in human bronchial cells. Probing these mechanisms may lead to the development of new antiviral drugs.

The virus also kills chicken embryos, unlike most human flu viruses. The polymerase genes are similar to those found in bird flu, including H5N1 in Asia, Taubenberger notes in the *Nature* paper. That means the 1918 flu likely arose from a bird virus and did not need to combine with a flu strain already adapted to humans to become so deadly.

Because of the sensitive nature of the work, the CDC lab's safety precautions received unusual scrutiny, says Tumpey, including review by several biosafety committees. Workers followed biosafety level 3 (BSL-3) practices, with additional enhancements, for instance, wearing battery-powered air purifiers with face shields and showering when leaving the lab. A year ago, Kawaoka's team drew fire for doing experiments with partial 1918 viruses under similar enhanced BSL-3

Handle with care. CDC's Terrence Tumpey wore a respirator as part of BSL-3 procedures for studying the recreated 1918 influenza virus. (*Inset*) A regular flu virus.

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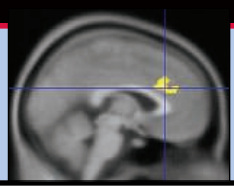

conditions, as opposed to the more stringent BSL-4 (*Science*, 22 October 2004, p. 591).

Since then, the government has weighed in, recommending in a draft biosafety manual that researchers use BSL-3 with additional measures for 1918 flu experiments. One reason BSL-4 isn't necessary, says government adviser Robert Lamb of Northwestern University in Evanston, Illinois, is that antiviral drugs are effective against 1918-like flu viruses. (CDC is also treating 1918 flu virus as a select agent, which means access is tightly controlled.)

Both the authors and *Science*'s editors acknowledge concerns that terrorists could, in theory, use the information to reconstruct the 1918 flu virus. Similar fears erupted 3 years ago when *Science* published a paper on the reconstruction of a poliovirus. *Science* decided to publish the 1918 flu paper because it "could help prevent another global flu pandemic," says Editor-in-Chief Donald Kennedy. That benefit "far outweighs the risk of working with this virus," he says.

In addition to regular scientific review, *Science* required the authors to show that they had approval to publish from CDC Director Julie Gerberding and National Institute of Allergy and Infectious Diseases Director Anthony Fauci. After being briefed, Health and Human Services (HHS) Secretary Michael Leavitt also requested that his new National Science Advisory Board for Biosecurity (NSABB) review the *Science* and *Nature* papers "to make sure we'd touched every possible base," said HHS spokesperson William Hall. After a flurry of e-mails and phone conferences last week, the panel suggested adding two sentences that underscore the stringent safeguards and the importance of the work in protecting public health.

The board's review surprised some scientists who expected NSABB to develop only general guidelines for journals. But Sam Kaplan of the University of Texas, Houston, publications chair for the American Society for Microbiology, says such reviews seem reasonable as long as they don't delay publication for months. "We certainly might turn to the NSABB" for a hot paper, he says.

–JOCELYN KAISER

U.S. BIOMEDICAL POLICY

Acting FDA Head Drops NCI Post

Trying to calm an uproar after he took a second job, the chief of the U.S. National Cancer Institute (NCI) declared last week that he would take a leave of absence while he serves as acting commissioner of the Food and Drug Administration (FDA).

President George W. Bush's appointment of NCI Director Andrew von Eschenbach on 23 September to succeed FDA's Lester Crawford drew an outcry from cancer researchers and several members of Congress, who argued that both agencies would suffer and that the two jobs posed conflicts of interests (*Science*, 30 September, p. 2142). Giving up the NCI job seems to allay at least some of those concerns.

The temporary NCI boss will be John Niederhuber, who came to the institute last month and this week became its deputy director for translational and clinical sciences. Niederhuber will also serve as "chief operating officer to handle the day-to-day management at NCI," according to memos von Eschenbach sent to FDA and NCI staff last Friday. Niederhuber, a surgical oncologist who has also studied cell signaling in tumors, most recently headed the department of surgery at the University of Wisconsin School of Medicine. Until July, he also was chair of NCI's National Cancer Advisory Board.

Niederhuber is "highly regarded in the oncology community," says David Korn, a senior vice-president at the Association of American Medical Colleges. As dean of Stanford University medical school, Korn hired Niederhuber in 1991 to head the surgery department. "I think it's a terrific opportunity for him and for the NCI," Korn says. Cancer biologist Tom Curran of St. Jude Children's Research Hospital in Memphis, Tennessee, is pleased as well. "John is an excellent choice for a challenging but important position at this critical time," says Curran.

Speaking anonymously, some cancer researchers said they were not disappointed that von Eschenbach, a friend of the Bush family who came to NCI 3 years ago from the University of Texas M. D. Anderson Cancer Center, is stepping aside from the research institute for the moment. His plan to eliminate suffering and death from cancer by 2015 has been criticized as wildly unrealistic. And his proposals for achieving it—initiatives on nanotechnology, proteomics, and tissue banking—have drawn a lukewarm response from NCI advisers. Meanwhile, success rates for obtaining basic R01 research grants are steadily declining. "I'm not sure [his tenure] will be seen as a great period in the history of NCI," said one academic researcher.

Within NCI, morale has slipped as budgets for intramural research have been trimmed and von Eschenbach built up a large personal staff that operated free of the established division directors, sources say. "It can't get much worse," said one senior scientist.

Fill-in. John Niederhuber will handle NCI's day-to-day business.

CREDIT: NCI

Even so, David Johnson, deputy director of the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, worries about how NCI will fare under an acting director, which "is about the most powerless position you can be in." Johnson wonders whether Niederhuber will "have the courage" to prioritize different NCI programs.

Von Eschenbach's memo says he "will not participate" in FDA matters involving NCI drug applications or clinical trials. But Johnson says that unless von Eschenbach resigns from NCI, his "residual interest" in the institution poses a potential conflict of interest. Another possible conflict, noted by *The Cancer Letter*, involves von Eschenbach's unpaid role as vice-chair of the board of C-Change, a nonprofit cancer advocacy organization headed by the president's parents, George H. W. and Barbara Bush. Its board members include drug industry executives.

–JOCELYN KAISER

With reporting by Jennifer Couzin.