Odd flu strain reveals its bag of tricks

Judging by looks alone, it's impossible to tell a mass murderer from the average person on the street. The same holds true for influenza viruses. Some strains merely cause an annoying flu; others inexplicably prove deadly on a staggering scale. For example, the strain that wreaked havoc in 1918 killed more than 20 million people worldwide.

Investigators seeking to understand such lethality have a new clue to puzzle over. Researchers in Wisconsin report a novel method by which one unusual influenza strain seems to expand the menu of cells in which it can replicate. This mechanism, however, does not resolve the mystery of the 1918 influenza, dubbed the Spanish flu.

Influenza viruses can infect both birds and mammals. They usually target specific organs of these animals, striking the intestines of birds and the respiratory system, primarily the lungs, of people and other mammals. This specificity arises because most influenza viruses require protein-cutting enzymes, called proteases, made only by cells of particular organ systems. The proteases cleave a viral surface protein called hemagglutinin, changing it into its mature form that allows the virus to attach to and infect cells.

In the past, scientists have observed that some influenza strains make a mutated hemagglutinin protein vulnerable to a wider range of proteases, including some that are ubiquitous within the body. Such viruses, which can infect many kinds of tissue, periodically devastate chicken populations.

Yet, the 1918 flu virus did not possess this lethal hemagglutinin mutation, according to a recent study of its genetic code (SN: 3/22/97, p. 172), and researchers have continued to look for other changes to explain influenza virulence.

Hideo Goto and Yoshihiro Kawaoka of the University of Wisconsin in Madison have examined a laboratory strain descended from the 1918 flu virus. The strain was produced in 1933 by infecting mice and isolating the viral mutants that could replicate in the animals' brains and other tissues.

Over the years, investigators have shown that this particular strain's wide-ranging infectious ability depends upon a second viral surface protein, neuraminidase. Moreover, they found that the strain cleaved hemagglutinin with a protease called plasmin, which is easily derived from plasminogen a precursor widely available in the host.

Goto and Kawaoka now have married those two pieces of evidence. In the August 18 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, they report that this influenza strain has alterations in neuraminidase that let it bind and sequester plasminogen. The virus thus has a ready source of plasmin, which it uses to cleave hemagglutinin. Less virulent influenza strains don't use their neuraminidase to help cleave hemagglutinin, they say.

While the influenza strain studied by Goto and Kawaoka has undergone extensive changes as a result of being grown in the laboratory for decades, researchers suspect that viruses in the wild may also employ neuraminidase. "I cannot believe this is the only virus in the world that uses this mechanism," says Kawaoka.

"This alerts people to the possibility that there is an alternative strategy for a virus to cleave hemagglutinin," agrees virologist Robert Webster of St. Jude Children's Research Hospital in Memphis, Tenn.

As for the Spanish flu, Jeffery K. Taubenberger of the Armed Forces Institute of Pathology in Washington, D.C., and his colleagues have sequenced about half of the neuraminidase gene from samples of the 1918 strain, including the areas highlighted by Goto and Kawaoka's work.

"The 1918 cases we've looked at don't have the mutations in neuraminidase, but it's still possible that an influenza virus in the future could use this mechanism," he says. "Flu viruses are always doing new and clever things." —*J. Travis*

Rhythm of the ice age: North versus south

R. Monastersky

A slice of ancient ice from Greenland.

Linked together like Siamese twins, Earth's northern and southern hemispheres should dance in tandem to the beat of climatic cycles. Indeed, every 100,000 years for the last million years, both halves of the globe have jointly entered into prolonged ice ages.

A close look at events within the last ice age, however, reveals that the two hemispheres often fall out of step with each other, sometimes even moving in opposite climatic directions, according to a team of European scientists. Their analysis of ancient ice from Greenland and Antarctica raises questions about what drove the ice-age temperature changes and whether similar factors are operating today.

"If we want to understand the climate today, we have to understand the climate of the past," says Thomas Blunier of the University of Bern in Switzerland.

Blunier and his colleagues studied ice cores pulled from a deep drill hole in central Greenland and from two drill holes in Antarctica. The ice in these places has piled up, layer by layer, over hundreds of thousands of years, preserving chemical clues to the climate of ancient times. By pulling up cores of this hoary ice, scientists can trace how conditions have changed.

During the last ice age, the climate in both hemispheres see-sawed from extremely cold to mild about every 3,000 years—a relatively quick swing by geological standards. Researchers have long wondered whether the warmings, called interstadials, happened simultaneously in the north and the south. They have had trouble, however, comparing the timing of the events in the records from the two hemispheres.

In the August 20 NATURE, Blunier and his coworkers describe a technique for matching up evidence of interstadials in the different ice cores. They focus on methane gas trapped in tiny bubbles of air from tens of thousands of years ago. Because worldwide concentrations of methane rose and fell markedly throughout the ice age, the researchers could use spikes in the ice's methane as benchmarks for lining up the three ice cores.

The new analyses of the matched cores showed that the short-term warmings during the ice age occurred at different times in Antarctica and Greenland. Temperatures in the south often rose a thousand years or more ahead of those in the north.

The work won praise from researchers studying other ice cores from Greenland and Antarctica. "They've taken timing to a new level," says James W.C. White, an ice-core researcher at the University of Colorado in Boulder.

Climate scientists have previously discovered hints that the northern and southern hemispheres did not always dance together as the last ice age ended. Wallace S. Broecker of Columbia University's Lamont-Doherty Earth Observatory in Palisades, N.Y., suggests that deep ocean currents in the far north and south may alternate in strength, cooling off one hemisphere while bringing warmth to the other—a pattern that agrees with the new discovery, he says.

One complicating factor has emerged from West Antarctica, however. Studies of a new ice core drilled there show climate fluctuations at the same time as those in Greenland, and therefore out of synch with the other Antarctic drill sites, says White. That leaves researchers with a cool conundrum to ponder. —*R. Monastersky*

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