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1918 Flu Virus Limited The Immune System

Body's Effort to Fight Was Often Deadly

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A Frankenstein version of the "Spanish flu" virus, assembled from parts in the laboratory, has shed new light on how the microbe killed tens of millions of people worldwide in 1918 and 1919.

Experiments in monkeys reveal that the 1918 virus came with the pre-packaged capacity to limit the immune system's ability to fight back in the first few days after infection. As the virus grows unchecked, the body attacks it with increasing quantities of highly toxic substances, which over time do as much harm to the host as to the invader. The result is often lethal damage to the lungs, where most influenza virus growth occurs.

The research provides further evidence that the 1918 virus had traits not found in other flu viruses and that it was the body's frantic effort to fight it that ultimately killed many victims.

"We know that the virus itself is different, and we know that the host response is different," said Yoshihiro Kawaoka, a virologist at the University of Wisconsin who headed the international research team.

"The virus is really a bad actor," said Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases.

The virulence of the 1918 virus has always been a mystery.

It was most lethal in young adults, the segment of the population usually most able to fight off severe infections. Many died a week or more after falling ill, with autopsies showing they had pneumonia caused by bacteria that had opportunistically infected virus-damaged lungs.

There were many reports, however, of people who died more quickly, occasionally even with a day of first symptoms. They presumably succumbed to the viral infection alone, and at autopsy their lungs were flooded with bloody fluid.

While many of the victims of bacterial pneumonia would be saved today with antibiotics, which didn't exist in 1918, there are still few treatments for the overwhelming viral pneumonia seen in Spanish flu. Consequently, understanding how it occurs on a molecular level is a high priority. That is especially true now, because the H5N1 "bird flu" strain of virus circulating in Southeast Asia has killed some of its 267 victims with viral pneumonia reminiscent of Spanish flu.

The experiment was done in a Canadian biosafety Level 4 lab, where researchers work in the equivalent of

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space suits. Kawaoka's team does not have permission to experiment with the virus in the United States.

Because of its extreme hazard, only a single group of U.S. researchers, at the Centers for Disease Control and Prevention in Atlanta, is currently allowed to use whole, living reconstructed versions of the pathogen that killed at least 50 million people nearly a century ago.

The new research, being published in the journal *Nature*, is possible because in 2005 American researchers successfully completed the laborious work of copying the 1918 virus's genetic blueprint, or genome, using fragments of tissue from three victims of the pandemic. That permits scientists to synthesize the microbe using a process called "reverse genetics," which Kawaoka developed in the 1990s.

In the new experiment, Darwyn Kobasa, a scientist in a Canadian government microbiology lab in Winnipeg, Manitoba, synthesized the 1918 virus from scratch and infected seven macaque monkeys with it. Three other animals were infected with a modern, far less virulent strain from the same large family of influenza A/H1N1 viruses.

The monkeys infected with the 1918 virus were so sick within eight days that they had to be euthanized. "Profuse watery and bloody liquid" filled 60 to 90 percent of the their lung tissue, "greatly reducing lung function," the researchers reported.

The scientists compared the amount of immune-system hormones, called cytokines and chemokines, produced by the two groups of monkeys.

The animals infected with the 1918 virus produced less interferon, a type of cytokine that suppresses virus growth by limiting the microbe's ability to infect new cells. The virus continued to replicate and spread, reaching in one case 5,000 times the levels seen in the tissue of the monkeys infected with the modern virus. The ability to selectively limit interferon production is seen in other microbes, including respiratory syncytial virus, Ebola virus and parainfluenza virus, Fauci said.

In response to the virus's unchecked growth, the monkeys' immune systems produced large amounts of inflammatory substances aimed at killing it and the cells already infected. That ultimately did lethal damage to the lungs of the animals.

In contrast, the animals infected with modern flu virus produced the full array of interferon compounds. The amount of virus in their tissues peaked and then declined rapidly. None died.

One theory for why Spanish flu preferentially killed young adults is that they are the age group with the most robust and reactive immune systems -- and therefore were most likely to mount a self-destructive response. Kawaoka, however, said his recent experiments do not directly address that idea.

One of the flu virus's eight gene segments, called NS1, appears to affect interferon activity and has also been implicated as one reason for H5N1 bird flu's lethality. It is an obvious target for further research, Kawaoka said.

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