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## Researchers Determine Reason for Deadly Spread of 1918 Influenza

The explosive spread of the influenza virus during the 1918 pandemic that killed some 20 million people worldwide was likely enabled by the unique structure of a protein on the virus's surface, researchers are reporting. The newly determined structure of the viral protein reveals that the 1918 strain of influenza underwent subtle alterations that enabled it to bind with deadly efficiency to human cells, while retaining the basic properties of the avian virus from which it evolved.

According to the researchers, although their findings do not apply to the new virulent strain of avian flu that is threatening to spread, they do emphasize how subtle alterations in the influenza virus's infectivity could spawn a major epidemic.

The findings were the result of a long-term collaboration between the late Don Wiley, a Howard Hughes Medical Institute investigator at Harvard University who died in an accident in 2001, and Sir John Skehel of the Medical Research Council's National Institute for Medical Research in London. Their studies were published February 5, 2004, in *ScienceExpress*, the online version of the journal *Science*.

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In their study, the researchers sought to understand the structure of the hemagglutinin protein, which covers the surface of the influenza virus and is known to initiate the first stages of viral infection. The protein does so by recognizing and binding to receptors on the cell surface that contain molecules called sialic acids. After hemagglutinin binds to these receptors, it causes pores to open in the human cells, allowing the virus to pass through.

According to Skehel, the researchers sought to understand how the 1918 version of hemagglutinin could bind to receptors on human cells, yet still retain many characteristics of its avian precursor virus.

“The 1918 virus was the first of this particular group of virus that caused a pandemic,” said Skehel. He said that the hemagglutinin in the 1918 virus was designated H1, and the influenza viruses that caused later pandemics had distinctively different hemagglutinin structures—designated H2 for the Asian influenza that began in 1957 and H3 for the Hong Kong strain, which began in 1968. “What was interesting was that, although all three of these subtypes came from birds, the H1 was quite different from H2 and H3, having hardly changed from what it was in the avian virus,” he said.

The researchers set out to explore this difference in detail, working from DNA sequence information that other researchers had gleaned from viral material isolated from autopsy samples preserved from the 1918 pandemic. Such scientific detective work was necessary because the virus had apparently gone extinct and had not been preserved in specimens from that era.

Using this sequence data, Wiley, Skehel, and their colleagues synthesized the gene for the H1 hemagglutinin and used it to produce the protein itself. They then crystallized the protein and used the analytical technique of x-ray crystallography to determine its structure.

“The structure revealed how this H1 group could still resemble the avian binding site, but nevertheless infect humans,” said Skehel. “We found basically that two sides of the hemagglutinin receptor binding site are in slightly different positions in the 1918 hemagglutinin, in comparison with the Hong Kong protein,” said Skehel. “This subtle difference allows the human receptor to bind in an antigenically favorable way.”

According to Skehel, the hemagglutinin of the current strain of avian flu that has killed people in Asia exposed to infected birds is closer to that of the Hong Kong flu. “But presumably, what's blocking this current flu from spreading person-to-person is that its hemagglutinin structure has not yet evolved such that it can efficiently infect humans,” said Skehel.

The researchers concluded that the hemagglutinin structure they uncovered for the 1918 virus may well have been a key contributor to its deadly spread. “With the ability to ensure the efficiency of the initial stages of virus infection, coupled with novel antigenicity, the human-1918 [hemagglutinin] may have been the prime determinant of extensive mortality in the 1918 pandemic,” the researchers wrote in *ScienceExpress*.