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VIROLOGY: From Two Mutations, an Important Clue About the Spanish Flu

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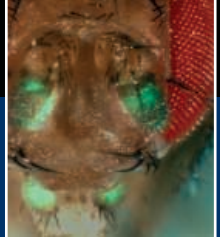

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VIROLOGY

From Two Mutations, an Important Clue About the Spanish Flu

HIV is lethal but not all that infectious; the common cold spreads easily but is fairly innocuous. The Spanish flu virus of 1918–1919 had the worst qualities of both, which is why it killed more people than World War I did. But although virologists have learned a lot about the combination of genes that made the virus so deadly, they could only speculate why it spread so easily.

No longer. A study published by *Science* this week (p. 655) confirms what many had suspected: A small change in the virus's hemagglutinin (HA)—a glycoprotein sitting on its surface by the hundreds—makes the 1918 virus more "avian" and unable to transmit between ferrets, even though it still sickened them. Those same changes in reverse may be what started the 1918 catastrophe—and what could kick off the next one as well.

"This is world news," says flu virologist Ron Fouchier of Erasmus Medical Center in Rotterdam, the Netherlands. "This answers the million-dollar question of how an avian virus can become transmissible between mammals." Still, exactly how the change in HA—which required just two point mutations—renders the virus impotent remains unclear, Fouchier says. Nor does it answer an even more urgent question: Could a similar set of mutations turn the bird flu virus H5N1, now devastating poultry in many countries, from an avian scourge into a human nightmare?

The HA in human flu viruses, such as the annual strains now sickening millions in the Northern Hemisphere, preferentially binds to a receptor on host cells that features a sialic acid bound to galactose through a linkage called α-2,6. This receptor predominates in both human and ferret airways. By contrast, avian viruses such as H5N1 have an HA with a slightly different shape that prefers to bind to a sialic acid linked to galactose through an α-2,3 link; these are in the majority in bird guts.

Based on that knowledge, researchers had suggested that the 1918 virus arose when an avian virus acquired mutations that gave it its predilection for α-2,6, thus becoming more "human" in nature. If so, reversing those mutations should be able to "avianize" the 1918 virus and make it unable to transmit among humans, says Terence Tumpey of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, the main author of the new study.

Small change. Two point mutations may have been enough to turn an avian virus into the 1918 flu, which killed more people than World War I.

So Tumpey, with colleagues at CDC and Mount Sinai School of Medicine in New York City, took the 1918 virus—which was resurrected over the past decade and is now the subject of intense study (*Science*, 7 October 2005, p. 28)—and made a few point mutations. One gave it an affinity for both the α-2,3 and α-2,6 receptors. One more switched its preference completely toward α-2,3.

When the researchers inoculated ferrets—the best animal model for human flu—intranasally with high doses of these two viruses, as well as the original 1918 strain, all three caused severe disease. But the ferrets to watch were those living in the cages next to the sick ones. With the original 1918 strain, they, too, became infected and got sick. With the strain that had a mutation that made it bind to both α-2,3 and α-2,6 receptors, transmission was inefficient; two out of three ferrets in adjoining cages developed antibodies, although neither became really ill. In the strain that bound to α-2,3 only, there was no transmission whatsoever.

The study provides the first direct evidence that receptor preference is key to transmission, says virologist Mikhail Matrosovich of the National Institute for Medical Research in London. But why a few point mutations can have such a dramatic effect is less clear, he says. Although α-2,6 receptors predominate in ferrets, they also have α-2,3 receptors, as do humans; that's why the avianized virus was able to infect them. So why couldn't this strain make the jump to the next cage?

One clue lies in studies last year that showed that human cells with α-2,3 receptors occur primarily deep in the lungs, from where the virus may not so easily escape. α-2,6 receptors, in contrast, were found primarily in the upper respiratory tract. Another hint is that the ferrets infected with the avianized virus didn't sneeze, Tumpey says; it's not hard to see why that would reduce transmission in ferrets.

Several groups, meanwhile, are trying to find out if H5N1, too, could become a humanized virus through a few mutations in HA. Mutations in other genes are probably necessary as well, says Yoshihiro Kawaoka of the University of Wisconsin, Madison, and the University of Tokyo, and if humankind is lucky, researchers may discover that the combination of changes needed is unlikely to occur in nature. But in any case, knowing in advance what it takes would give scientists something to be on the lookout for in dead birds and human patients, Fouchier says—and ring the alarm bell if necessary.

–MARTIN ENSERINK

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