5,040 words

INFLUENZA

Feature Article

Prepared for

Laboratory Medicine

by

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August 19, 1998

Influenza: A Modern Plague

The epidemic hit suddenly, beginning as an ordinary attack of flu and rapidly developing into a deadly pneumonia. As a doctor at the scene described it in a letter to a friend,[1] healthy young soldiers were suddenly stricken and "*dropped like flies.*"

"Two hours after admission [to the hospital] they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face. . .It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible.

"For several days there were no coffins and the bodies piled up something fierce, we used to go down to the morgue and look at the boys laid out in long rows. It beats any sight they ever had in France after a battle. . .it would make any man sit up and take notice to walk down the long lines of dead soldiers all dressed and laid out in double rows."

The year was 1918. The epidemic hit Camp Devens, near Boston, in early fall and lasted more than four weeks. Each day it killed about 100 soldiers. Special trains were used to carry the dead. The 50,000 soldiers at the camp were completely demoralized.[1]

This pandemic infected a large proportion of the world's population, killing about 2.5% of those afflicted — a mortality rate *25 times higher* than the rate in the usual influenza epidemic. The disease was dubbed the "Spanish flu" because of many early deaths in Spain. We now know a better term would have been "swine flu," because the virus has since been traced to swine.

Although usually the influenza virus is only a severe nuisance, the respiratory disease it causes is highly contagious. The virus causes an epidemic almost every year,

infecting 10% to 20% of the U.S. population. About 20,000 Americans die in each epidemic, most of whom are elderly or debilitated. The death toll in the U.S. may be even higher in some years during a more severe epidemic. Pandemics occur less frequently. The 1957 Asian flu pandemic killed about 70,000 Americans; the 1968 Hong Kong flu pandemic killed about 34,000 Americans.

The much higher death rate in the 1918 influenza pandemic was due to an exceptionally virulent virus, which killed a disproportionate number of young people, providing further evidence that it was different from the usual virus. Lack of antibiotics and other effective treatments for secondary infections may have been a factor, but many young victims died from an overwhelming, primary viral pneumonia *within hours of the first symptoms, before a secondary infection could have occurred*.

If virologists knew why the 1918 virus was so deadly, they might be better able to predict whether newly emerging strains will be deadly. Toward this end, viral RNA recovered from tissue samples of three people who died from influenza in 1918 is currently being studied at the Armed Forces Institute of Pathology. Two of the samples are histology specimens taken at autopsy from U.S. soldiers and embedded in paraffin 80 years ago. The third was from the exhumed, frozen body of an Alaskan Eskimo.

This pioneering work is being done by a team headed by Jeffery K. Taubenberger, MD, PhD, Chief, Division of Molecular Pathology, Armed Forces Institute of Pathology, Washington D.C. According to Dr. Taubenberger, “The genomes are very, very fragmented. The largest pieces of RNA are about 150 nucleotides in length. But we can consistently amplify and sequence the small fragments of the influenza genome, and can ultimately piece everything together and get the entire genome. We found from the little

fragments, as indicated in our publication in Science,[2] that the virus was clearly influenza A, H1N1 subtype. The sequences that matched it best were from the earliest human and swine influenza viruses isolated in the 1930's.

"It seems clear there was a first wave of influenza in the spring of 1918. It was highly infectious," continues Dr. Taubenberger, "but not very lethal, and there were no descriptions of pigs being sick. There's also very good historical evidence that in the fall, a lethal variant emerged that caused the really bad pandemic, and humans and pigs got sick at the same time. It could be that the virus went from humans to pigs, although there's no way to prove that. All three of our isolates were from people infected in the second wave. We'd love to find some first-wave cases, but there were not many deaths in that wave."

The Nature of the Disease

The "flu" virus is spread by aerial droplets and inhaled into the pharynx or the lower respiratory tract. Infection can be asymptomatic, or can progress to an unpleasant illness or even a rapidly fatal viral pneumonia.

After an incubation period of one to four days, symptoms typically appear: headache, chills, a severe, dry cough, and possibly chest "tightness" and soreness. Coryza (runny nose) is often absent. Contrary to popular terminology, "stomach flu," or "24-hour flu," is not caused by the influenza virus. In fact, gastrointestinal symptoms are uncommon in influenza.

In a day or two after infection, coughing begins and the temperature rises to 38 °C to 40 °C, accompanied by significant myalgia, malaise, and anorexia. The fever begins to

abate in another day or two, but the cough often becomes more intense. The disease gradually resolves over a one- to three-week period.

Interferon and other cytokines are released in response to the infection and seem to constitute the initial defensive reactions. Interferon-α and interleukin-6 appear to cause the fever, headache, myalgia, and malaise that start in the second day of the disease.[3] Lasting immunity develops, but only after two to three weeks, so the immune response does not play a defensive role in the acute infection. Immunity gives lifetime protection against reinfection by the same strain of virus — but not against new strains.

The Influenza Virus

Influenza virus is classified as an *Orthomyxovirus*, named for its ability to adhere to mucus in the airways and lungs. Virions are about 100 to 2200 nm in diameter, and the surface envelope is composed of lipid materials partly derived from the membrane of the infected cell. About 500 antigenic protein molecules, either neuraminidase (N) or hemagglutinin (H) in a ratio of 1 to 5, cover the envelope.

Viral hemagglutinin provides the molecular structure for the virus to attach to sialic acid in the cell's membrane. The hemagglutinin determines to which type of cell the virus can attach and infect. The amino acid sequence of the hemagglutinin is characteristic of the species to which the virus is adapted, and corresponds to the specific molecular structure of the sialic acid in the cell's membrane.

For the virus to be infective, the hemagglutinin must be cleaved by a proteolytic enzyme usually present in the airways. How easily the hemagglutinin is cleaved is related to the infectivity of the virus. Inclusion of trypsin in culture medium cleaves the

hemagglutinin and permits influenza virus to be grown in cultured cells that would otherwise be resistant to the virus. Neuraminidase is responsible for release of the virus from cells after the infective cycle. It, too, plays a role in host specificity.

Inside the envelope, a matrix protein layer encloses the RNA that makes up the viral genome. The RNA is surrounded by nucleoprotein. The various proteins of viral strains may differ, providing a way to distinguish strains by immunological tests. Although the segments of the viral RNA genome appear upon electron microscopy to form a single unit, each segment is biologically independent.

Current Nomenclature

Influenza A viruses are designated based on the antigenic properties of their neuraminidase (N) and hemagglutinin (H) spikes. The antigenic subtypes are numbered sequentially: H from 1 to 14, and N from 1 to 9. Individual strains of virus, as used in vaccines, are designated more descriptively. For instance, “A/Mississippi/1/87(H3N2)” indicates an influenza A virus, isolated in Mississippi, the laboratory’s identification number of the isolate (optional), the year it was isolated, and the antigenic subtypes. Nonhuman strains include the host of origin. Designation is the same for influenza B and C strains, but without the antigenic subtypes.