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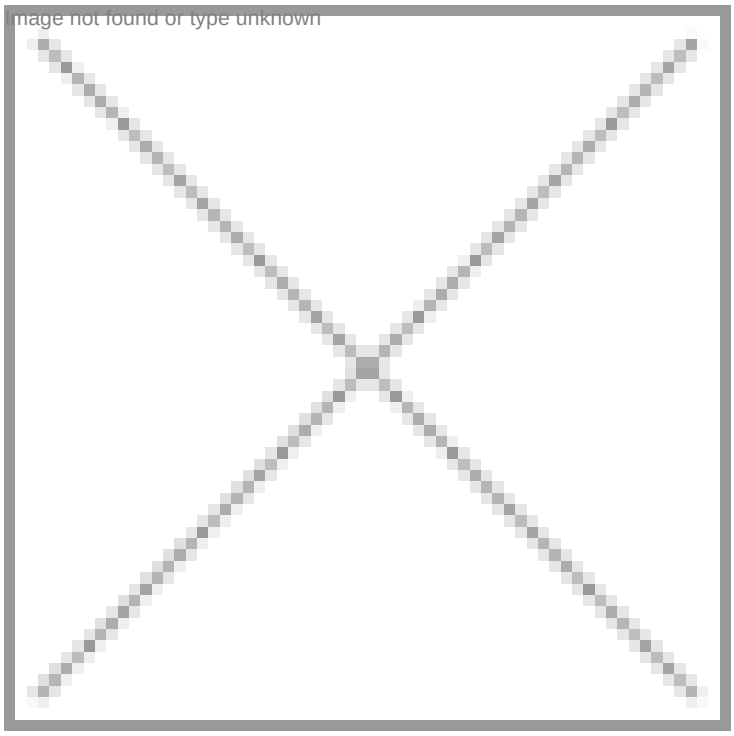

Reviving the virus of 1918 flu

In an attempt to understand the nature of influenza pandemics, scientists have revived the virus that caused the flu of 1918, raising many questions.

"It is simply a struggle for air until they suffocate" (Grist, 1979) - a physician who treated influenza patients during the 1918 flu pandemic.

The 1918 flu was the worst pandemic to hit mankind in recorded history, a scourge that killed more than 20 million (some reports put the number at 50 million) people worldwide. More people died of influenza in a single year than the four years of Black Death Bubonic Plague from 1347 to 1351. Yet has a disease of such mammoth proportions that occurred in recent history been largely forgotten?

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Not really, if recent reports are any indication, especially since experts have warned the possibility of another devastating pandemic and the need to be prepared for it.

And in the quest for that preparedness, scientists have brought back the 1918 influenza virus to life! A team of scientists headed by Terrence Tumpey, a research scientist at Centers for Disease Control and Prevention (CDC) in Atlanta, USA announced the reconstruction of the virus that caused the deadly 1918-19 pandemic. The work was done in collaboration with Mount Sinai School of Medicine, Armed Forces Institute of Pathology and Southeast Poultry Research. The findings were published in the October 7 issue of Science.

The landmark research has identified genes and characteristics, which were responsible for making the 1918 virus so virulent. It is expected to help in understanding the mechanism for generation of pandemic strains. It will help in the development of new therapies and vaccines to protect against another such pandemic.

Says Professor Garcia-Sastre chief investigator of the project at Mount Sinai Hospital, "The significance of the reconstruction of the 1918 flu virus is to understand the genesis of a pandemic. Now will the H5N1 become pandemic? Nobody knows. People say that mutation from avian to human is inevitable, I don't know where people get that information. But if we know what makes a virus pandemic we can optimize surveillance for emerging strains and be on the alert when we see pandemic-like quality appear in the virus."

Scientists are hopeful that the study will throw light on how a virus, which normally remains stable in birds, develops into such a deadly strain in humans. Influenza pandemics occur when a new strain emerges to which people have little or no immunity. There have been four influenza pandemics in the recorded history: 1890, 1918,1957 and 1968.

Most experts fear the outbreak of another pandemic but nobody is sure about the timing, type of strain or the severity of such a calamity.

Mapping the reconstruction efforts

This real possibility of a pandemic spurred the scientific community to launch the drive for preparedness. For this, scientisists had to find out the mechanisms by which the virus becomes deadly and spreads from human to human. The eight genes which made up the interior of the 1918 influenza viral particle or its genetic sequence had to be deciphered.

Initially scientist thought that the virus could be recovered from the frozen lungs of dead victims of 1918 pandemic buried in Alaska. However, they found that the virus was too fragile to remain intact and hence that attempt failed.

A more prudent approach was to find the genetic code which will reveal the secret of its virulence. This time the source was the frozen lung specimen of a soldier who died in September 16, 1918, that was stored in the tissue repository of the Armed Forces Institute of Pathology (AFIP).

Using a technique called Polymerase Chain reaction (PCR), scientists at AFIP were able to extract influenza RNA fragments from the lung tissue. They reported the initial results of genetic characterization of the 1918 Spanish influenza virus in the March 1997 issue of Science. The group from AFIP reported on the details of the final three genes in 2005, October issue of Nature, thus characterizing the complete genetic sequence (Genome) of the 1918 virus.

Jeffery Taubenberger was the lead author of the sequencing study. According to their analysis, the 1918 virus was derived from the avian influenza virus. The virus causing the 1957 and the 1968 epidemics acquired their pathogenecity by reassortment of the genes between an avian influenza strain and the then circulating human strain. Reassortment occurs when two different influenza strains infect a cell and a hybrid virus gets generated that contains genetic materials from both viruses.

The 1918 virus, however, was not generated by reassortment but was wholly derived from virus that originally infected birds. Simply stated it was a bird virus, which acquired the capability of infecting humans and spreading from one person to another. The current avian flu viruses have also infected humans but the potential to spread among humans is low. Scientists fear that in due course the virus may adapt and acquire such an ability leading to another 1918 like pandemic.

Scientists at Mount Sinai hospital in New York worked to transform the code into genes by using Taubenberger's blueprint. The reconstruction of the virus was done using a molecular technique called "reverse genetics". This technique was developed and patented by Drs Adolfo Garcia- Sastre and Peter Palese that creates viruses from DNA and is widely used in laboratories that work on influenza. Reverse genetic enable researchers to quickly build custom viruses.

The final reconstruction of the viable virus and tests on the mice for its pathogenecity were done at the laboratory in Centers for Disease Control and Prevention (CDC). In reconstructing the virus, the team of researchers headed by Dr Terrence M Tumpey, a senior microbiologist at CDC, experimented on various combinations of genes. In this process they found out the genes which made the virus so deadly. The reconstructed virus was used to infect the mice and after just 4 days it replicated to produce thousands of virus particles. The mice lungs were flooded by the virus particles and all the mice died within 6 days of infection with the reconstructed 1918 virus.

To do or not to do: the ethical question

The paper raised a lot of debate in media. The need to resurrect a lethal virus, which could potentially escape and play havoc, was questioned by media and experts alike. Whether the benefits outweighed the risks of this recreation was hotly debated. So what are the risks? The 1918 flu virus was extremely virulent, perversely affecting the young and healthy population between the ages of 15-34. Flu is a seasonal disease and during such seasonal outbreaks, complications and death occur in the very young and the very old.

Skeptics fear two issues: what if the virus escapes from the laboratory? Firstly the chance of virus escaping is very low. The work has been done in laboratories with Animal Biosafety Level 3 practices with special enhancements. Biosafety level 3 practices include a combination of stringent containment measures and procedures for protection of personnel, environment and the community. Well, theoretically, the virus, if it escapes, can lead to a disaster.

"But in reality it wouldn't have the same consequences as the 1918 pandemic. There is some residual immunity to the 1918 virus present in a portion of human population. Moreover current anti-virals and vaccines are effective against the 1918 virus," says Garcia-Sastre. In fact the research staff at the CDC took prophylactic antiviral medications to protect them.

The second concern relates to the issue of bioterrorism. What if terrorists use is as a tool with the availability of the blueprint for this virus. This concern is also widely ruled out as a pandemic will strike indiscriminately affecting all nationalities as it spreads across the globe.

Some experts are skeptical about the utility of such an exercise. They say that a systematic risk-benefit analysis has not been done. According to them the statements about the benefits are too general and do not provide a concrete evidence of the benefits. The research is more about basic understanding of the virus than any direct health benefits. According to them, the added value of one additional strain of influenza virus is very limited.

Most experts feel that the next pandemic strain will emerge from an avian influenza strain. The article in Science also validates this theory. The results of this research, skeptics not withstanding, will immensely help in the ongoing efforts at the preparedness for the next pandemic.

Not surprisingly, the paper about the reconstruction of the 1918 Spanish flu, "Characterization of the reconstructed 1918 Spanish Influenza Pandemic virus" published in the October issue of Science and "Characterization of the 1918 influenza virus polymerase genes" published in the Nature were awarded as the Paper of the year, 2005 by The Lancet.

Balaka Aggarwal in New York