*17 November 2009*

*This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.*

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## Chem-Bio News – Pandemic Influenza Edition #87

**1. STUDY SHOWS LINK BETWEEN INFLUENZA VIRUS AND FEVER:** *"In most cases it is cytokines which trigger the fever. "We have now been able to show, for the first time, that RIG-I also cranks up the production of a central cytokine in the case of a virus infection," Dr. Hendrik Poeck explains."*

**2. PATHOLOGICAL CHANGES ASSOCIATED WITH THE 2009 H1N1 VIRUS:** *"On autopsy for all five patients, the right and left lungs had increased in weight (650 to 1200 g for each lung; normal, 450 g) and had a solid consistency ….. In four patients, zones of edema, hemorrhage, or necrosis were observed in the upper respiratory tract on the internal surface of the larynx and trachea, as reported in previous cases of seasonal influenza. All five patients showed evidence of pulmonary damage and signs of acute interstitial lesions, as noted in patients with avian influenza A (H5N1) virus infection."*

**3. SCIENTISTS PUT INTERACTIVE FLU TRACKING AT PUBLIC'S FINGERTIPS:** *"The researchers linked many powerful computer systems together to analyze enormous amounts of genetic data collected from all publicly available isolated strains of the H5N1 virus – the cause of avian flu. They then developed a new Web-based application that will allow health officials and the public visualize how the virus moved across the globe using Google Earth."*

**4. THE NS1 PROTEIN OF THE 1918 PANDEMIC INFLUENZA VIRUS BLOCKS HOST INTERFERON AND LIPID METABOLISM PATHWAYS:** *"The 1918 NS1 gene may therefore have contributed to the virulence of the 1918 pandemic virus by disrupting the innate immune response, inducing hypercytokinemia, and by blocking the transcription of certain lipid-based proinflammatory mediators that function as part of the host antiviral response."*

# CB Daily Report

## Chem-Bio News

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### STUDY SHOWS LINK BETWEEN INFLUENZA VIRUS AND FEVER

Infection Control Today Magazine
November 16, 2009

“In most cases it is cytokines which trigger the fever. “We have now been able to show, for the first time, that RIG-I also cranks up the production of a central cytokine in the case of a virus infection,” Dr. Hendrik Poeck explains. He and his colleagues Dr. Michael Bscheider and Dr. Olaf Groß are the primary authors of the study. This is a reference to interleukin 1, probably the most important cytokine known today.

Do cytokines cause more severe courses of a disease?

When RIG-I comes into contact with a virus gene, it does two things. On the one hand, it ensures that certain immune cells produce pro-interleukin, the precursor of interleukin 1, en masse. At the same time it activates an enzyme via a complicated signaling pathway which transforms pro-interleukin into interleukin 1. "This interleukin 1 then ensures that the typical symptoms of a virus infection such as fever or shivering occur," professor Veit Hornung from the Bonn University Clinic explains.”

The full article can be found at: http://www.infectioncontroltoday.com/hotnews/link-between-flu-virus-and-fever.html

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**PATHOLOGICAL CHANGES ASSOCIATED WITH THE 2009 H1N1 VIRUS**
By M. Virgilia Soto-Abraham, M.D., Juan Soriano-Rosas, M.D., Alberto Díaz-Quiñónez, Ph.D., Juan Silva-Pereyra, Ph.D., Patricia Vazquez-Hernandez, M.D., Oralia Torres-López, M.D., Alfonso Roldán, M.D., Ana Cruz-Gordillo, M.D., Patricia Alonso-Viveros, M.D., Francisco Navarro-Reynoso, M.D.
New England Journal of Medicine
November 12, 2009

“Between April 23, 2009, and May 15, 2009, we performed 15 autopsies on deceased patients in whom probable influenza had been diagnosed either clinically or macroscopically. Small samples of lung tissue were obtained and taken for analysis to the Institute of Epidemiological Diagnosis and Reference in Mexico City. Five infections with the 2009 pandemic influenza A (H1N1) virus were confirmed with the use of a real-time reverse-transcriptase–polymerase-chain-reaction assay, after it was determined that these patients were seronegative for influenza B virus, respiratory syncytial virus, parainfluenza virus (types 1, 2, and 3), and adenovirus.1 From these five patients, organ samples were collected, fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. In the remaining 10 patients in whom the 2009 H1N1 virus was not detected, histopathological analyses identified bacterial pneumonia.

All five patients with diagnosed 2009 H1N1 influenza had been residents of Mexico City. Four of them were young adults (ages 22, 26, 28, and 37 years) who were hospitalized with the presumptive diagnosis of influenza. These patients were initially treated with antibiotics for bacterial pneumonia. The fifth patient was an 83-year-old woman with a diagnosis of

cerebral hemorrhage, who had no clinical signs of influenza but showed characteristics of hemorrhagic pneumonia on macroscopic evaluation. The patients had died 7 to 13 days after the onset of influenza symptoms.

On autopsy for all five patients, the right and left lungs had increased in weight (650 to 1200 g for each lung; normal, 450 g) and had a solid consistency (see Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In four patients, zones of edema, hemorrhage, or necrosis were observed in the upper respiratory tract on the internal surface of the larynx and trachea, as reported in previous cases of seasonal influenza.2,3 All five patients showed evidence of pulmonary damage and signs of acute interstitial lesions, as noted in patients with avian influenza A (H5N1) virus infection.3,4

In four patients, we observed hyaline membranes, alveolar septal edema, hyperplasia of type II pneumocytes, fibrin thrombus in the vascular lumen, and necrosis of the bronchiolar walls; three patients had inflammatory infiltrate below the endothelium and partial loss and adherence of the endothelium in the medium- and small-caliber intrapulmonary blood vessels (Figure 1). These histologic changes are characteristics of influenza though not pathognomonic. In three patients, we observed pneumonia foci with intraalveolar exudates without evidence of bacterial colonies; however, nearly all the patients had received antibiotic treatment. In two patients, we observed erythrophagocytosis and phagocytosis of inflammatory cells in the liver, spleen, and bone marrow, which is similar to observations in lethal cases of infection with the avian influenza A (H5N1) virus2 (Fig. 2 and 3 in the Supplementary Appendix). One patient had focal centrilobular necrosis of the liver and hemorrhagic necrosis of the adrenal gland cortex, and acute tubular necrosis was observed in another patient."

The full article can be found at: http://content.nejm.org/cgi/content/full/361/20/2001

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**SCIENTISTS PUT INTERACTIVE FLU TRACKING AT PUBLIC'S FINGERTIPS**
Infection Control Today Magazine
November 16, 2009

"The researchers linked many powerful computer systems together to analyze enormous amounts of genetic data collected from all publicly available isolated strains of the H5N1 virus – the cause of avian flu. They then developed a new Web-based application that will allow health officials and the public visualize how the virus moved across the globe using Google Earth.

The resulting visualizations, based on results of the data analysis, represent the most comprehensive map to date of how avian flu has been transmitted among sites in Asia, Africa and Europe.

But underlying those findings is a new way of analyzing genetic data that generates more complete information about the flu's spread. The method, combined with the increasing

availability of sequenced genomes of isolated flu strains, is expected to help public health officials make more knowledgeable predictions about how the H1N1 flu pandemic will evolve."

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"The visualizations and application are available online at http://routemap.osu.edu. The research appears online in the journal Cladistics.

But in this paper, the researchers used the power of supercomputers to generate millions of phylogenetic trees representing relationships among these thousands of viruses. They then picked a pool of thousands of high-quality trees based on a scoring system in the bioinformatics field to use in their analysis of disease transmission."

The full article can be found at: http://www.infectioncontroltoday.com/hotnews/interactive-flu-tracking.html

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**THE NS1 PROTEIN OF THE 1918 PANDEMIC INFLUENZA VIRUS BLOCKS HOST INTERFERON AND LIPID METABOLISM PATHWAYS**
Drug Week
November 20, 2009

"The ''Spanish influenza'' of 1918 claimed an unprecedented number of lives, yet the determinants of virulence for this virus are still not fully understood. Here, we used functional genomics and an in vitro human lung epithelial cell infection model to define the global host transcriptional response to the eight-gene 1918 virus."

"To better understand the role of the 1918 virus NS1 gene, we also evaluated the host response to a reassortant 1918 virus containing the NS1 gene from A/Texas/36/91 (a seasonal isolate of human influenza virus), as well as the host response to a reassortant of A/Texas/36/91 containing the 1918 NS1 gene. Genomic analyses revealed that the 1918 virus blocked the transcription of multiple interferon-stimulated genes and also downregulated a network of genes associated with lipid metabolism. In contrast, the expression of genes encoding chemokines and cytokines, which serve to attract infiltrating immune cells, was upregulated. Viruses containing the NS1 gene from A/Texas/36/91 induced a significant increase in type I interferon signaling but did not repress lipid metabolism."

"The 1918 NS1 gene may therefore have contributed to the virulence of the 1918 pandemic virus by disrupting the innate immune response, inducing hypercytokinemia, and by blocking the transcription of certain lipid-based proinflammatory mediators that function as part of the host antiviral response."

The full article can be found at: (R. Billharz, et. al., "The NS1 Protein of the 1918 Pandemic

Influenza Virus Blocks Host Interferon and Lipid Metabolism Pathways". Journal of Virology, 2009;83(20):10557-10570). Link not available.

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