Up in the Air

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Breathing with Birds

Recently, spread of an avian flu virus has thrown public health worldwide into panic. Historically, pandemic influenza viruses pose a significant threat to humans.[1] In the twentieth century, three influenza viruses emerged that caused major pandemics: the 1918 Spanish flu virus (killed an estimated 20 to 50 million people worldwide), the 1957 Asian flu virus, and the 1968 Hong Kong flu virus (both of which killed between 0.5 and 1 million people in the United States alone).

The emergence of a new threat led scientists Taubenberger et al.[2] to sequence and phylogenetically analyse the complete genome of the 1918 influenza virus. They assembled the sequences of the eight gene segments of the 1918 pandemic virus from RNA fragments obtained from paraffin block and frozen tissue of several victims of the 1918 virus. They report the entire gene sequence of the virus and show remarkable similarities between the polymerase genes of the influenza virus that caused the 1918 Spanish influenza pandemic and those of subsequent avian influenza viruses. Additionally, they confirm that the 1918 Spanish influenza virus was not a reassortant virus (like the 1957 and 1968 viruses) but rather was an entirely avian-like virus that became adapted to humans through mutation. This means that currently circulating, highly pathogenic avian influenza viruses could evolve into human pandemic viruses either through gene reassortment or through direct mutation of viral genes.

Simultaneously, Tumpey et al.[3] successfully reconstructed the deadly 1918 pandemic virus in mice and showed that it kills mice faster than any other influenza virus so far tested. The purpose of this landmark experiment was to ‘understand more fully the virulence of this virus and possibly of other human influenza pandemic viruses.’ As the threat of the emergence of another pandemic virus is considered likely, characterization of the 1918 virus may help recognize the potential threat posed by new influenza virus strains, and direct us towards appropriate prophylactic and therapeutic countermeasures that will be needed to control pandemic viruses.

The currently circulating avian H5N1 strain is genetically similar to the 1918 Spanish virus[1]. Russell and Webster[1] believe that 'the substantial number of human cases caused by the H5N1 strain of avian influenza virus over the past two years (118 reported cases and 61 deaths), some clusters of probable human-to-human transmission, and the similarity to 1918 pandemic influenza virus all suggest that the only remaining trait for H5N1 to acquire to become a pandemic virus is efficient human transmissibility.' This poses a viable threat as the geographical range of migratory birds has increased and the H5N1 strain is already endemic in migratory birds.

1. Russell CJ, Webster RG. The Genesis of a Pandemic Influenza Virus. Cell. 2005; 368-71.
2. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature 2005; 437: 889-93.
3. Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solo´rzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, Garci ´a-Sastre, A. Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. Science 2005; 310: 77-80.

Feeding the Lungs

Studies for therapy through diet for cancer patients have been inconclusive due to several confounding variables. However, the fact that cruciferous vegetables protect against lung cancer is consistently evident from observational studies. Recently, Brennan et al. published a large study in the Lancet elucidating the role of cruciferous vegetables in lung cancer after stratifying by GSTM1 and GSTT1 status, two genes implicated in the elimination of isothiocyanates. Isothiocyanates are phytochemicals which

have been shown in animals to have strong chemopreventative properties against lung cancer.

The authors conducted a case-control study of 2141 cases and 2168 controls from six countries of central and eastern Europe, a region that has traditionally high rates of cruciferous vegetable consumption. In addition to GSTT1 and GSTM1 genotyping, all participants completed a standardized food frequency questionnaire. Weekly consumption of cruciferous vegetables protected against lung cancer in those who were GSTM1 null (odds ratio=0·67, 95% CI 0·49-0·91), GSTT1 null (0·63, 0·37-1·07), or both (0·28, 0·11-0·67). No protective effect was seen in people who were both GSTM1 and GSTT1 positive (0·88, 0·65-1·21). Similar protective results were noted for consumption of cabbage and a combination of broccoli and brussels sprouts. In terms of frequency of consumption, an overall protective effect was seen for consumption of cruciferous vegetables at least once a week compared with less than monthly. When the population was stratified by smoking history (never vs ever), the protective effect in never smokers was largely independent of GSTM1 and GSTT1 status, being recorded in those who were positive for both M1 and T1 (0·31, 0·14-0·70) and negative for M1 and T1 (0·12, 0·01-1·54). This study provides further substantial evidence for a protective effect of cruciferous vegetable consumption on lung cancer.

1. Brennan P, Hsu CC, Moullan N. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomization approach. Lancet 2005; 366: 1558-60.

Sleep Apnea, Stroke and Death

The obstructive sleep apnea syndrome is a treatable form of disordered breathing in which the upper airway closes repeatedly during sleep. The syndrome is associated with vascular risk factors and with substantial cardiovascular morbidity and mortality. It has been suggested previously that obstructive sleep apnea is an important risk factor for stroke, however, the role of other dependent variables (such as hypertension and smoking) in this association was not clear.

Yaggi et al[1] recently published a study in the NEJM based on their hypothesis that patients with the syndrome have an increased risk of stroke or death from any cause that is independent of other cerebrovascular risk factors. They designed an observational cohort study, in which patients underwent polysomnography, and subsequent events (strokes and deaths) were verified. The diagnosis of the obstructive sleep apnea syndrome was based on an apnea-hypopnea index of 5 or higher (five or more events per hour); patients with an apnea-hypopnea index of less than 5 served as the comparison group.

Among 1022 enrolled patients, 697 (68 percent) had the obstructive sleep apnea syndrome. After adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death (hazard ratio, 1.97; 95 percent confidence interval, 1.12 to 3.48; P=0.01). The authors conclude that the obstructive sleep apnea syndrome significantly increases the risk of stroke or death from any cause, and the increase is independent of other risk factors.

1. Yaggi HK, Concato J, Kernan WN. Obstructive Sleep Apnea as a Risk Factor for Stroke and Death. N Engl J Med 2005; 353: 2034-42

Cystic Fibrosis (CF) - more than one disease

Though originally thought to be a single disorder of Mendelian inheritance, CF has been shown to have a vast spectrum of clinical presentation depending of the mutation ranging from severe pulmonary compromise and meconium ileus to rhinosinusitis and male infertility.[1] Recently it was shown that this spectrum was not only governed by the type of CFTR gene mutation, but also by modifier polymorphisms in other genes.[2] The Gene Modifier Study Group analyzed genetic polymorphisms in several candidate genes for two groups of CF patients: those with severe pulmonary compromise and mild pulmonary disease, based on FEV1 values (cutoff = 68% predicted FEV1). They found that a codon 10 polymorphism of TGF-beta1 strongly associated with severe pulmonary disease (P=0.0002). This polymorphism was associated with low FEV1 on quantitative analysis as well. The study demonstrates that modifier genes can alter the presentation of even a monogenic disease such as CF.

1. Badano JL, Katsanis N. Beyond Mendel: an evolving view of human genetic disease transmission. Nat Rev Genet. 2002;3:779-89.
2. Drumm ML, Konstan MW, Schluchter MD. Genetic modifiers of lung disease in cystic fibrosis. N Engl J Med. 2005 6;353:1443-53.

Asthma Patterns

Frey et al published a recent study analyzing the patterns of bronchoconstriction in asthmatics treated with short acting beta2-agonist, albuterol, compared to long-acting salmeterol.[1] Twice daily peak expiratory flow rates (PEFR) were followed up in 80 non-smoking subjects for three 6-month treatment periods: Placebo, Albuterol and Salmeterol. The 300 data points in each period were analyzed using a special mathematical algorithm from chaos theory and fractals called detrended fluctuation analysis to obtain the bronchoconstriction pattern of each patient. This variable called alpha was compared between the three treatment groups. The study found that salmeterol decreases the risk of airway obstruction compared to placebo, whereas

albuterol increases the risk by increasing the chaos in the pattern of bronchoconstriction. This pattern is distorted with increasing severity of asthma as well. Using further mathematical modeling Frey et al, designed an equation to predict the precipitation of an asthmatic attack in a patient within 1 month based on the PEFR values at any point in time[1].

1. Frey U, Brodbeck T, Majumdar A. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. Nature. 2005;438:667-70.

Science Lens

From Fame to Fire with Fraud

It was not a happy ending to 2005 for editors of some of the world's highest ranked scientific journals, like Science and Nature. The breakthrough research in stem cells published by Dr. WS Hwang and colleagues from Seoul[1-3] in these two major journals was unveiled as fabricated and fraudulent.

This event marks one of the biggest scientific cons of all time. South Korean scientist Woo-suk Hwang, was a scientist previously lionised as a pioneering genius, particularly in his native South Korea, where he was given the title 'Supreme Scientist.' His cleverly reported experiments on the world's first cloned human embryos (11 stem cell lines) were found to be fabricated and so was his claim to have produced the world's first cloned dog, Snuppy.

The peer review process has been brought into question by this development, with claims that reviewers were unable to judge the authenticity of the data presented. However, those who visited Dr. Hwang's lab after the publication of these papers to learn more about the landmark research experiments had little doubt too that the reports were not based on sound data. Those who later tried to replicate the same experiments found crucial errors and fallacy, precipitating academic and legal investigation into the matter.

Dr. Hwang resigned from his position at Seoul National University, and has been stripped of all the fame and respect that once accompanied his name. He now faces serious charges in South Korea, condemnation by the international academic community and the public at large.

1. Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK. 2005. Patient-specific embryonic stem cells derived from human SCNT blastocysts. Science 2005; 308: 1777-1783.
2. Hwang WS, Ryu YJ, Park JH, Park ES, Lee EG. Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst. Science 2004; 303: 1669-1674.
3. Lee BC, Kim MK, Jang G, Oh HJ, Yuda F, Kim HJ, Shamim MH, Kim JJ, Kang SK, Schatten G, Hwang WS. Dogs cloned from adult somatic cells. Nature, 2005; 436:641.