Medical Hypotheses (2006) **67,** 1006–1015

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medical hypotheses

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Editorial

Bird flu, influenza and 1918: The case for mutant Avian tuberculosis

Summary Influenza is Italian for ''influence'', Latin: influentia. It used to be thought that the disease was caused by a bad influence from the heavens. Influenza was called a virus long, long before it was proven to be one. In 2005, an article in the New England Journal of Medicine estimated that a recurrence of the 1918 influenza epidemic could kill between 180 million and 360 million people worldwide.

A large part of the current bird-flu hysteria is fostered by a distrust among the lay and scientific community regarding the actual state of our knowledge regarding the bird flu or H5N1 and the killer ''Influenza'' Pandemic of 1918 that it is compared to. And this distrust is not completely unfounded. Traditionally, ''flu'' does not kill. Experts, including Peter Palese of the Mount School of Medicine in Manhattan, remind us that even in 1992, millions in China already had antibodies to H5N1, meaning that they had contracted it and that their immune system had little trouble fending it off. Dr. Andrew Noymer and Michel Garenne, UC Berkely demographers, reported in 2000 convincing statistics showing that undetected tuberculosis may have been the real killer in the 1918 flu epidemic. Aware of recent attempts to isolate the ''Influenza virus'' on human cadavers and their specimens, Noymer and Garenne summed that: ''Frustratingly, these findings have not answered the question why the 1918 virus was so virulent, nor do they offer an explanation for the unusual age profile of deaths''. Bird flu would certainly be diagnosed in the hospital today as Acute Respiratory Distress Syndrome (ARDS). Roger and others favor suspecting tuberculosis in all cases of acute respiratory failure of unknown origin.

By 1918, it could be said, in so far as tuberculosis was concerned, that the world was a supersaturated sponge ready to ignite and that among its most vulnerable parts was the very Midwest where the 1918 unknown pandemic began. It is theorized that the lethal pig epidemic that began in Kansas just prior to the first human outbreaks was a disease of avian and human tuberculosis genetically combined through mycobacteriophage interchange, with the pig, susceptible to both, as its involuntary living culture medium. What are the implications of mistaking a virus such as Influenza A for what mycobacterial disease is actually causing? They would be disastrous, with useless treatment and preventative stockpiles. The obvious need for further investigation is presently imminent and pressing.

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doi:10.1016/j.mehy.2006.05.002

The Hygienic Institute, Innsbruck, Austria, 1901

Scientist Alois Lode, having just isolated fowl plague, now known to be fowl or H5N1-like bird influenza ''virus'', saw it pass through a filter. Through this, Lode, first professor of the new chair of Hygiene at the University of Vienna, established the prototype for all subsequent filterterable animal virus studies. Yet, Lode insisted that just because bird flu passed through a filter did not mean that it *wasn't* a bacteria [1].

Haskell Country, Kansas: Autumn of 1918

It had to be more than a coincidence that by the autumn of 1918 thousands of Midwest pigs died, seemingly from the same flu-like illness and in the same location in which the worst human pandemic in history was about to begin. US Inspector and veterinarian J.S. Koen, much to the chagrin of the pork industry, insisted that not only was he seeing pigs get the same ''flu-like'' illness as human victims, but that he had actually seen the two species interinfect one another. Koen, for lack of an another term, called this unknown disease in pigs swine ''influenza'', even as it killed pig after pig. Koen knew better.

That thousands of pigs died in the Autumn of 1918 was only complicated by the fact that bird or fowl TB also called Avian tuberculosis or *Mycobacterium avium* could infect birds as well as hogs and cattle. . . . . .and humans. And to round out this picture, human *M. tuberculosis*, although primarily affecting humans, could also be transmitted to hogs and cattle. So tuberculosis struck at will and affected all warm blooded vertebrates, the atypical strains other than human tuberculosis apparently getting into humans through the respiratory tract [2]. Also unknown at this time, but pertinent since Kansas lies squarely in America's ''dustbowl'', were the results of a European experiment wherein guinea pigs exposed to organisms like Avian tuberculosis got little or no lung disease. However, when these mycobacteria were placed in dust aerosols, guinea pigs came down with progressive, fatal lung disease, not unlike what was occurring in the pandemic of 1918 [3]. Thus, though it has been proposed that infection with fowl tuberculosis requires some ''defect'' in the human immune system, that defect could be as simple as dust tying up the body's defenses. Certainly a previous tuberculosis infection, common in 1918, with or without accompanying ''chronic bronchitis'' would be, in certain cases, more than enough to qualify many as ''compromised host'', unleashing an animal or soil non-tuberculosis mycobacterial infection. Expert Rosenzweig found a surprising number of these cases were in younger adults free of coexisting disease [4]. Rosenzweig isolated a case of Fowl tuberculosis (*M. avium* intercellular) in human lungs [5], commenting, that, although the average case of fowl TB in humans was thought to involve host compromise, that otherwise healthy hosts could also be affected in which severe and progressive diseases would and did occur. *Mycobacterium kansasii* and certain forms of *M. avium intercellulare* are the commonest forms of non-human tuberculosis in human (lungs).

But why, besides the fact that *M. avium* and *M. kansasii* were in abundance, should everything have begun in Kansas? This probably was a result of the history of the epidemiology of human tuberculosis, one of the pre-requisites of becoming an immunocompromised host. Although the present pandemic of human TB began in 16th century England it reached its peak in 1780 as a result of industrial revolution and the spread of cities, which allowed person to person spread. It then traveled rapidly to other large western European cities,

reaching a second peak in the early 1800s. It was only by the mid and later 1800s that North and South American waves spiked. Furthermore, peak mortality rates for New England in the US came first and it was only with industrial development that the US epidemic traveled to the Midwest years later and finally the West [2].

So by 1918, it could be said, in so far as tuberculosis was concerned, that the world was a supersaturated sponge ready to ignite and that among its most vulnerable parts was the very Midwest where the 1918 unknown pandemic hit, in rural Haskell country, Kansas, in the midst of this pig slaughter, a few hundred miles from Camp Funston, today Fort Riley. America had already entered World War 1. And though consensus has it that the lethal epidemic of 1918 began in Camp Funston, as early as January, Dr. Loring Miner of Haskell Country was already knee-deep in the medical struggle of his life. A disease of unknown origin, progressing to fulminating pneumonia, was cutting down dozens of the strongest and most robust around him. And although Haskell was just a place where people, hogs, poultry, earthen sod houses, cattle, and manure melded into one, Miner would try to see to it that this small rural epidemic got national attention, through the April 1918 issue of what today is called *The Morbidity and Mortality Weekly Report*. If it was influenza, which at that time wasn't considered lethal enough to be a reportable disease, it wasn't acting like any influenza Miner had ever seen, killing otherwise strong men and women indiscriminately. Minor's report was the warning, but went unheeded. While the Haskell epidemic ended as abruptly as it had begun, soon disease spread to Army barracks in nearby Funston. It would subside, but come back in the fall with a vengeance. Camp Funston in March, camp Devens in September, then across the country and the world, leaving an estimated 50–100 million dead globally, at least 600,000 to a million of them American, in the span of less than a year, the most destructive plague that man had ever witnessed.

US Department of Agriculture, Washington, DC, 1917

The situation had become so grave in hogs and cattle that by 1917, one year before the most destructive pandemic ever, the Cooperative State-Federal Tuberculosis Eradication Program, administered by the US Department of Agriculture (USDA) and Animal and Plant Health Inspection Service (APHIS), had to be instituted. For in 1917 it was estimated that 25% of deaths from tuberculosis in adult humans were caused by animal tuberculosis [6].

Although pigs could be infected by human tuberculosis as well, the most prevalent tuberculosis found in their autopsied bodies was far and away fowl or bird tuberculosis (*M. avium*), which affected a wide range of bird species, including water fowl, migratory birds, and domesticated birds as well as a number of mammals [7]. In some cases sudden death could even occur in a bird with normal body weight and outer appearance. Avian tuberculosis was then as now a problem of unknown magnitude, mainly due to the lack of reliable diagnostic tests. Pigs had therefore involuntarily become the living laboratory thru which two of the main types of tuberculosis could mutate through the genetic exchange by their viral bacteriophages, much in the same fashion as has been attributed to ''Influenza''. The stage was set for disaster.

Just as men get infected, bacteria can get infected and the small tadpole shaped viruses that do this are called *bacteriophages*, viruses that infect regular bacteria and *mycobacteriophages*, viruses that infect tuberculosis, which is a mycobacteria. Or both can be called simply ''phages''. Bacteria reproduce asexually so there is no variation of genes in a colony, and no way for them to exchange genetic material. Phages, the viruses which live inside bacteria such as the mycobacteria called tuberculosis, can allow exchange of this genetic material, as well as force natural selection. The way bacteriophages or ''phages'' allow gene diversity is after they insert their own genetic material into their bacterial prey's genome, they in essence highjack the manufacturing capacity of the bacteria for their own purposes, reproducing new viruses in the bacteria. However, when a virus makes copies of itself, sometimes it extracts some of the bacteria's DNA and copies that into the virus. When these viruses infect other bacteria, usually of the same class, such as from bird tuberculosis to human tuberculosis inside the pig, they add the other bacteria's genes to the new bacteria. This creates genetic diversity or ''mutations''. Such genetic ''mutations'' can create far more virulent bacteria then either of the parent bacteria. This is what it is theorized happened in 1918 Haskell Country, Kansas, where genetic elements of human and avian tuberculosis combined inside hogs just prior to the pandemic of 1918.

However, this is not all that phages instigate. If the devil where to work overtime in a plot to confound scientists in their quest for a causative agent to a serious disease of unknown origin, it is doubtful whether he could have come up with anything

better than the phage. Attaching to the outer membrane of the bacteria with apparatus like a space landing gear, phages often times disrupts the cell membrane of say avian or human tuberculosis, which according to Pickett [8] causes much of these species ''cell-wall-deficient'' forms, often tiny fragments of varied shapes which easily pass through the smallest filters and therefore seem to be viral, yet as bacterial fragments aren't. Some of these shapes such as the frequently seen filamentous forms of tuberculosis mentioned by Corper [9] are similar to those attributed to ''Influenza'' by biochemist and Influenza guru Burnet [10]. Burnet, the first and for a time the only virologist in Australia, even conceded that there are bacteria with viral forms in Q-fever [11] and earlier in this same article, *Virology as an Independent Science*, relates that chemical studies of purified viruses show that they are composed of the same sorts of material as bacteria. He includes Influenza here although refers to the fact that it ''probably has no DNA'' (Ibid.). But, according to Xalabardar, some cell-wall-deficient mycobacterial forms also are exclusively RNA. Furthermore, points out Xalabarder, such cell-wall-deficient tubercular forms are true antigens, all of which, similar to Influenza, induce the production of specific antibodies detectable by complement fixation tests, yet cannot produce a positive TB skin test [12]. In time such fragments can and do regenerate to the original classical form of the germ but are infective even before doing so. If this were not enough, phages also disrupt known staining patterns whereby a pathogen such as tuberculosis, which classically stains and is thus identified by being ''acid-fast'' (does not lose its red color when acid alcohol reagent is applied), often looses this capacity when fragmented by phages into its ''cell-wall-deficient'' viral forms, resulting in either not staining acid-fast at all or doing so intermittently, at which point they are called ''variably acid-fast''. It is little wonder then why scientists could easily mistake bacterial elements for viruses, and all because of the actions of bacterial viruses called ''phages'' on their bacterial prey.

In 1923, Richard Shope showed that people who were alive during the 1918–1919 epidemics had antibodies against the pig ''virus'', but those born after 1920 lacked such antibodies [13].

War Department, Medical Board, US Army, May, 1918

Lieutenant Dr. Bill Welch was both disgusted and embarrassed. What he had just read grated on his nerves. His chief, Surgeon General William Gorgas had again both ironically and foolishly been quoted for calling ''Influenza'' a phrase borrowed directly from John Bunyon's reference to tuberculosis, namely: ''This greatest of all the captains of the men of death'' [14]. Welch at one time had studied under Koch, the German discoverer of tuberculosis. Tuberculosis (TB), although on the decline still threatened, in 1918, the life of every man, woman and child in most American cities. A diagnosis of tuberculosis still meant almost certain death and during the years 1900–1950 it is estimated that TB killed 5 million Americans. Furthermore, during this span, the death rate was twice as high among men, the exact ratio in the Pandemic of 1918. Even more tellingly, as TB mortality fell at the end of the Pandemic, more so did the various forms of pneumonia directly implicated in it. Welch had read that New York's Shuyler Center had just loaned their tuberculosis staff to the American Red Cross to help organize and direct a 3 months emergency campaign against influenza in New York, New Jersey, and Connecticut at a time when they could least afford to do so with five new tuberculosis hospitals and eight new TB dispensaries scheduled to open in 1918. No, the current epidemic wasn't just influenza, thought Welch. Nor did he believe those who speculated a ''filterable virus'' which passed thru a porcelain or clay filter. These reports had not been reproducible.

In what today would surely be called Acute Respiratory Distress Syndrome (ARDS), and unlike any flu ever known which usually struck the very old and very young, this disease broke all the rules. It wasn't just a deadly infectious disease, It was a deadly infectious disease with the singular and terrifying quality of being better at killing men and women in their prime, between 20 and 40, than the old and the infirm. As early as 1900 it was already obvious that although young adults were dying of TB routinely, there was extremely low mortality between the ages of 5 and 15 [15]. Besides, Influenza typically came in the winter, this one began in the late spring and summer, Welch also realized, first hand, that this ''Influenza's'' clinical symptoms truly shocked medical officers across the country. Instead of the usual flu, which gave mild to moderate fever, Patients could spike to 105° or 106° with accompanying delirium. Instead of the sore throat, cough and various joint aches and pains, patients bled from the nose and ears, expectorated bloody, foamy sputum, became blue from lack of lung oxygen delivery, at which point it was only a matter of hours away from death thru suffocation from pneumonia, a horrible death [16]. At some army camps there averaged 100

deaths per day and upon autopsy, sliced blue swollen lungs exuded bloody froth, causing Pathologists to say, over and over again that this must be some kind of new disease for certainly it wasn't Influenza. The War Department knew that it was the pneumonia and not the influenza that was doing the killing, they just had no idea what was causing the pneumonia. All of these signs and symptoms have subsequently been documented in the literature on disseminated tuberculosis and atypical tuberculosis but it proved simply overwhelming at the time it was happening. The first autopsy of a victim occurred in Chicago in April. The pathologist doing it was besides himself seeing the lungs full of hemorrhages and troubled enough to mention to the Editor-in Chief of *The Journal of Infectious Diseases* ''to look over it as a new disease'' [17]. Yet, Gorgas insisted on referencing ''influenza'' an old and heretofore not that deadly disease.

To be certain the spectacle of witnessing several autopsies was too much, even for William Henry Welch, a seasoned pathologist and top medical lieutenant in Gorgas's Executive Committee of the General Medical Board [18]. Welch knew that surveys made in and around 1918 revealed that almost all adults in Europe and America were tuberculin positive, having at some time been infected with the bacilli. Into this situation now came a seemingly new unknown disease, which, like tuberculosis, once in army camps thrived on fatigue, exposure and crowding. It certainly was acting like a mycobacteria. Was it a combination involving Avian tuberculosis? One 1918 army medical officer had aptly mentioned to him that ''Whenever you mobilize and call to the colors a 1000 men, you call with them at least 20 billion tubercle bacilli, 10 billion typhoid, 5 billion pneumonia, and a couple of million dysentery germs'' [19]. But what that medical officer failed to mention was that of these only TB specifically could and did routinely cause ''pneumonia''. Villemin, who even before Koch, established the infectious nature of tuberculosis and as a military surgeon, wrote about the increased incidence of TB in soldiers and medical personnel in barracks, compared it to a similar disease transmitted from horse to horse at army depots [20]. Previously, Welch became a leader in the anti-tuberculous campaign based on Koch's germ theory of disease. Welch was probably the first in the United States to demonstrate the tubercle bacillus to students, at Bellevue Hospital in New York. But the problem Welch was having was that the relationship between TB and Influenza wasn't clear to most and he wasn't about to stick his neck out. True, at most centers TB patients died at a considerably higher rate after getting Influenza, but at least one institution reported there was less influenza in their tuberculosis patients [21]. As William Welch and officers and scientists of the War Department frantically searched for a cause, America was stunned into a medical nightmare such as it had never known.

Camp Devens, Massachusetts Surgical Ward, 29th September 1918

In 1918, Camp Devens, near Boston was supposed to have 50,000 men, or did have before the epidemic broke loose. Starting with a flu-like illness in what appeared to be grippe or Influenza, soldiers brought to the hospital seemed to quickly develop the most viscous type of pneumonia ever recorded. Two hours after admission mahogany spots appeared over their cheekbones leading within hours to a blue cyanosis extending from their ears to spread all over the face until racial differentiation was impossible. From that point, it was only a matter of hours until death came, following the struggle for air and suffocation. Camp Devens was now seeing close to 100 such deaths a day, including an outrageous number of doctors and nurses among them.

Even In the early 1800s consumption was the most frequent cause of recognized death in New England, and particularly in Boston, site of a major outbreak of the new pandemic. By 1918, tuberculosis was still widespread and deadly, continuing to head the list of fatal contagious diseases, despite the fact that it was kept off most death records, both because it left entire families stigmatized and ostracized, and, the fact that many cases were misdiagnosed. A favorite alternative diagnosis was ''pneumonia''. Yet in certain 1918 Army medical screening units 1 in 5 recruits had either tuberculosis or venereal disease. In 1901, just 17 years before the Pandemic of 1918, A.S. Knopf of Philadelphia wrote *Tuberculosis as a Disease of the Masses and How to Combat It*, eventually translated into 27 languages and selling more copies than any other publication besides the Bible. Christmas seals sold to raise money for the fight against tuberculosis and sponsored by the American Red Cross were by 1919 finally transferred to the National Tuberculosis Association. This was the backdrop for the Pandemic of 1918 by an unknown Infectious agent.

In the early phase of any new TB epidemic, perhaps from a new strain, tuberculosis manifests itself as an acute, generalized disease, and only much later the chronic pulmonary tuberculosis we

know in today's Western world. An example can be found in the high mortality during the ''Influenza'' pandemic, when African American's were brought to fight in France during the World War I, large numbers of them dying from the accelerated tuberculous ''galloping consumption'' of yesteryear. There has been much documentation that in certain cases, depending on the virulence of the tubercular strain, that the infection can spread rapidly, causing a disease both acute and fatal, with signs and symptoms so unspecific that a proper diagnosis is impossible to make. Today such fulminating tuberculosis occurs mostly in Latin America and Asia [15]. At all times in the history of man, tuberculosis has manifested itself with extreme violence and destructiveness when it attacks populations newly exposed to it or a new strain of it, particularly in groups of people compelled to live under wartime conditions, even in places not exposed directly to hand-to-hand combat, including America. It increased suddenly and dramatically everywhere in Europe within a very few months after the beginning of World War I. And frequently during the War, we are talking tuberculosis with a rapid fulminating course, generalized as well as meningeal, in exactly the same fashion as the many cases of ''meningitis'' attributed to the ''Influenza'' of 1918. Incredibly, and as a precise measure, the tuberculosis rates during WWI, which began to rise in 1915, with the onset of war, were even higher than when TB was thought to certainly be destroying the civilization of Europe in the early 1800s. And suspiciously, TB rates plummeted exactly at the time ''Influenza'' did at the succession of that War in 1919 [15]. Thus was the fine line that humans walked on the planet in coping with the obviously endemic many evolving strains of tuberculosis.

The Pathological Society of Great Britain and Ireland, London, England, 1922

The damage had been done and the world buried its millions when Donaldson [22] tried to put the pieces together. From the preceding epidemic, that of 1890–1891, it had become clear that Pfeiffer's Bacillus, only discovered after the addition of hemoglobin to culture media, before which it too was thought to be a ''virus'', had not caused the Pandemic of 1918. At this point the medical world was ready to accept as causal any organism which could claim the distinction of being new to bacteriology, even if it's constant relationship could not be proved. To this effect Donaldson ended his 174 page expose with the statement that Pfeiffer's bacillus could not be the cause of influenza, quickly adding that there was not ''the slightest shred of evidence that the disease is due to a so-called filter-passing virus''.

Department of Animal and Plant Pathology, The Rockefeller Institute for Medical Research, New York, 1931

Nevertheless, virologists saw a great opportunity provided by the 1918 pandemic and by hook or by crook would prove it to be viral. Richard Shope began the first salvo working on swine ''influenza'', again falling back on the stale conception that the mild disease and flu-like symptoms created in pigs by what he felt to be a filterable virus [23]. Shope had the singular advantage of realizing that since 1918, pigs had been coming down with the same ''Influenza'' each year. But beginning his investigations in earnest, Shope became perplexed. Not a virus, but a bacteria kept cropping up in swine's mucous secretions and it resembled the Pfeiffer's bacillus or *Haemophillus Influenza* (H. Flu) more than anything else. The problem was he couldn't infect most of his subjects with the bacteria. So he took the mucous secretions of sick pigs and put it thru a filter which he felt would only yield a virus. However, incredibly, even the filtrate from the discharge just gave low grade symptoms. So if it wasn't a ''virus'' that had caused the deadly strains of flu and it wasn't a bacteria which, although present in most malignant ''flu'', even upon serial passage, didn't infect healthy subjects, what could it be? To Shope, possibly both, working in conjunction with one another. So he introduced both into animals which subsequently came down with just the deadly ''flu'' complicated with pneumonia that killed between 20 and 100 million people in 1918. What Shope was not aware of was that, although Lord had found the bacillus in only 3 or 20 ''flu'' cases in studies of the 1907–1908 epidemic, he had also found Pfeiffer's bacillus in 30% of cultures from TB patients. Quickly following this, in 1933 and this time in England, Smith, Andrews, and Laidlaw took the cue, this time ''proving'' that human influenza could be transferred to animals called ferrets with something that passed through a filter and supposedly without a bacterium. Then cross immunity tests showed that whatever the agent was, which Smith, Andrews, and Laidlaw insisted was a ''virus'', it had strong antigenic similarities between its form in pigs and in humans. But in truth, until the late 1940s influenza viruses

were studied as infections, which, although filterable, were conceived of as analogous to bacteria, a kind of ultrabacteria.

Not to be deterred, and still seeing Influenza as a great opportunity for virology, in 1941 virologist Hirst [24] claimed that influenza ''virus'' could agglutinate red blood cells of fowl and other animal species. Hirst showed that ''virus'' particles first adsorbed to the red cells and, after a certain time, eluted again as a result of what could be interpreted as an enzymatic reaction. But 6 years later, Middlebrook and Dubos (1948) made this seem nothing more than a cheap hat trick by showing that similarly red blood cell agglutination could be produced by sera from patients with tuberculosis [25]. Takahashi and Ono then reviewed similar red cell agglutination occurring in the presence of tuberculous serums [26,27].

Headquarters of The American Medical Association, Chicago, Illinois, October 9, 1926

Calling the unknown disease that killed thousands of Midwest pigs in the Autumn of 1918 would by no means be the first time that tuberculosis had been called the TB virus or flu, as it was just 8 years prior to 1918, when Fontes mentioned that in certain circles, filterable, flu-like factions of human and animal tuberculosis were often referred to as ''the TB virus'' [28] and Koch himself, when delivering his now famous lecture and demonstrations regarding the TB bacilli, not only began by calling it the TB virus, but had almost as hard a time convincing the German medical establishment that it was indeed a bacterium as gaining their acceptance of the bacillus by his many demonstrations [29]. In fact articles circa 1918 refer to ''virus'' as infectious, but not distinctive from bacteria. Rather the term ''virus'' had the same usage and application as bacillus. And when Nicolle and Lebailly [30] did the very first experiments pointing to a ''filter-passing-virus'' as Influenza's true cause in 1918, the filters used could have just as easily let many virus-sized bacterial forms that they were unaware of pass through.

Seven years after the most vicious infectious epidemic ever to hit the United States, this issue came up again. Upon the direct invitation of the Journal of the American Medical Association (JAMA), a panel which consisted of three of the foremost experts on tuberculosis in the United States sat around a roundtable, discussing an important JAMA article entitled *Mutation Forms Of The Tubercle Bacilli*. Medical doctor HC Sweeny, author of the paper, had already presented before the AMA's 77th session in Dallas earlier that year. Sitting across from Sweeny was legendary researcher Esmond R. Long, a physician also from Chicago. Rounding out this expert panel of three was Dr. H.J. Corper of Denver, head of TB research at the National Jewish Hospital, Denver. All three men had gone thru and survived the Pandemic of 1918 and what they were discussing today was crucial in that Sweeny had found filter-passing virus-like mutations, not of Influenza, but of tuberculosis. Furthermore, such mutations generated mere fragments of the TB bacilli that somehow, with time, grew back to the bacillus's traditional form [31].

Long began the discussion by saying that if the panel didn't know the care with which Sweeny worked, they might be inclined to think that he was seeing contaminants, but that Long knew how constantly Sweeny kept contamination in mind and worked meticulously against it. Besides, the organisms to which Sweeny referred did not resemble in any way the common contaminating air organisms. Long went on to mention that there were many concomitant French reports regarding the same viral-like tuberculosis mutants. Long then intriguingly brought up that it was possible that some of these small forms as well as the similarly viral-like tuberculosis granules found earlier by Much might just be pieces of the TB bacillus. But what made these pieces of extreme importance was their ability to spring back and regenerate into their traditional form. The possibility existed in Long's read of Sweeny's work that this regeneration from fragments was of much importance in several areas. Clearly, the possibility existed that effects attributed to a ''filterable virus'' such as ''Influenza'' were really the result of filter passage by cell fragments capable of regenerating classic life-threatening tuberculosis once they passed the filter.

At this point Corper divulged a regularly found form of pathogenic tuberculosis studied at the National Jewish Hospitlal with egg medium whereby a large number of long filamentous uniformly staining acid fast bacilli, the same configuration as that written up for Influenza. Long's eyebrows raised noticeably upon hearing this. Sweeny ended the roundtable by confirming his vigilance against contamination and his most interesting finding: just how small a portion of tubercle bacillus or granule may be, passing the finest filter, before it went on to produce septicemia in laboratory animals and finally reverted to classical tuberculosis. Confirmation of Sweeny's work and its extension into the

many virus-like forms of Avian tuberculosis was written up by experiments Mellon and Fisher did 6 years later, in 1932, in *The Journal of Infectious Diseases* in 1932 [32].

University of California, Berkeley, September 2000

In a 16 page paper which appeared in Population And Development Review demographers Andrew Noymer and Michel Garenne came up with convincing statistics showing that undetected tuberculosis may have been the real killer in the 1918 flu epidemic [33]. Aware of attempts to genetically characterize the 1918 virus through samples from human bodies preserved in permafrost and paraffin embedded autopsy material of 1918 victims, investigations aimed solely at looking for a virus [34,35]. Noymer and Garenne summed their thoughts this way: ''Frustratingly, these findings have not answered the question why the 1918 virus was so virulent, nor do they offer an explanation for the unusual age profile of deaths''.

Conclusion

In 2005, Professor Roy Anderson, a leading infectious diseases expert and chief scientist of England's Ministry of Defense, warned that Bird Flu could put Britain in quarantine, closing offices and schools across that country.

There is an old adage which rings particularly true for even state of the art science. It reads: ''You get what you look for''. It is also a trap, that no scientist should fall into. Specifically, if you are looking for a viral cause for the lethal Pandemic of 1918 and ignoring any evidence of bacteria or mycobacteria such as Avian tuberculosis, either on a historical, pathological, microscopic or serum assay level, you will undoubtedly eventually come to the conclusion it was a ''virus''. You will not only ignore evidence of bacterial disease in specimens but you will use agents such as phenol which can kill every bacteria that crawls. You will be sure that the ''virus'' passes a filter, get a good photomicrographic picture of it, and since it has antigenic properties, like all infectious pathogens, develop and use reagents and compliment fixation tests, all of which you will correlate with ''known'' variations of ''viruses'' to once and for all nail down your argument. But does that mean that in reality what you have seen and labeled a virus is in certainty a virus. Not at all. The public, with its vital scientific funding, would rather hear that their great–great grandfather died from or was threatened by an Influenza or a virus in 1918 than by the killer tuberculosis any day. For one, perhaps, if it was TB, then it could have been passed, from generation-to-generation, to themselves. And so scientists, as well as many physicians, reflexively have to magnify viruses importance to survive. What has been the funding to find and identify the virus-like forms of tuberculosis or bird tuberculosis? Fractional, if at all, compared to the funding available for viral studies on Influenza alone.

The fact that Influenza virus prior to and after 1918 put up nothing to compare with the lethality of the killer pandemic to such investigators will be immaterial. The fact that tuberculosis killed an estimated 1 billion people by itself [42] between 1850 and 1950, the approximate midpoint of which was the pandemic, is immaterial. The fact that the interchange of tuberculosis with its atypical forms such as Avian tuberculosis can produce lethal new mutants leading to multi-drug-resistant strains like when in 1990, a new multi-drug-resistant (MDR) tuberculosis outbreak took place in a large Miami municipal hospital is immaterial. Or that events soon thereafter, with similar outbreaks in three New York city hospitals, left many sufferers dying within weeks — also immaterial. By 1992, approximately two years later, drug-resistant tuberculosis had spread to seventeen US states, with mini-epidemics in Florida, Michigan, New York, California, Texas, Massachusetts, and Pennsylvania and was reported, by the international media, as out of control. This too becomes unimportant. The only thing that does become important is that, yes, you were right, it's a ''virus''. Never mind that there are infectious fragments of typical and atypical tuberculosis which can simulate and appear the same as these ''viruses'' in everyway. Never mind the historical context in which the killing fields of 1918 took place. Never mind the demographic, epidemiologic and historical proof that it was not Influenza A that did the killing. Never mind that tuberculosis itself often presents with flu-like symptoms. And never mind that Influenza A could have been the innocent passenger virus in 1918 as Barr-Epstein, and Cytomegalovirus were in AIDS.

Yet a large part of the current bird-flu hysteria is still fostered by a distrust among the lay public as well as many scientists regarding the actual state of our knowledge regarding the ''bird flu'' or ''H5N1'' and what really was behind the killer ''Influenza'' Pandemic of 1918 that Bird Flu is often compared to. And this distrust is not completely unfounded. For instance experts, including Peter

Palese of the Mount School of Medicine in Manhattan, remind us that even in 1992, millions in China already had antibodies to H5N1 meaning that they had contracted it and that their immune system had little trouble fending it off.

It was in 1952 that Cornelius P. Rhoads, Director of the Sloan-Kettering Institute for Cancer Research in New York City remarked in the introduction to a conference on *Viruses and cancer* that the term ''virus'' had achieved ''a high professional status with doubtful credentials'' [36]. And as van Helvoort aptly points out, by the 1950s the word ''virus'' had become so mouldable a concept that one could speak of *virus* workers without the existence of any consensus whatsoever of what viruses were [37]. Extremely supportive of this mouldability among virologists was Max Delbruck's subtitle for *Virus, 1950*, a conference held at the California Institute of Technology, called: *Proceedings of a conference on the similarities and dissimilarities between viruses attacking animals plants and bacteria* [38]. Indeed, in the 1930s and 1940s the concept of ''filterable virus'' was subjected to such criticism that its very foundations were threatened. Statements like those coming from pioneer virologist Andre Lwoff in 1957 such as: ''viruses should be considered as viruses because viruses are viruses'' were totally unacceptable [39]. Also under the gun was Thomas M. Rivers, the Father of American Virology, who said you could differentiate viruses by three things, namely, their invisibility under the ordinary microscope, their ability to pass the finest filters because of this small size, and their inability to propagate themselves in the absence of susceptible cells [40]. But many, many scientists disagreed. Twort, working on Johne's bacillus, presently itself suspected of being a mycobacterium, had to add special factors before this bacteria would grow on a lifeless medium and Sweeny's *JAMA* study which showed that certain virus-like forms of tuberculosis met Rivers criteria as well. Rivers was wrong. In fact Klieneberger-Nobel showed just the opposite, that some bacteria could pass through filters that some of the larger viruses could not [41].

To say the history of the theoretical underpinning of Virology has been a tortuous one, is probably an understatement and, incredibly, many virologists, even to this day, persist in using the flawed reasoning that that which passes thru a microfilter is a virus. Should the Pandemic of 1918 return, what are the implications of mistaking a virus such as Influenza A for what mycobacterial disease is actually causing? They would be disastrous, with useless treatment and preventative stockpiles, and moreover, precious time wasted. The obvious need for further investigation is presently imminent and pressing.

References

[1] Lode A. Zur Biologie des Erregers der Huhnerpest (Kyanolophia gallinarum). Centralblatt fur Bakteriologie, Parasitenkunde und Infektionskrankheiten, Abr 1, Orig. 1907;xliii:355—9. p. 357.

[2] Schlossberg D. Tuberculosis praeger mongographs in infectious disease, vol. 2. New York: Prager Scientific; 1983.

[3] Tacquet Gernez-Rieux C. An experimental study of interactions between Pneumoconiosis and mycobacterial infections. Ann NY Acad Sci 1972;106.

[4] Rosenzweig DY. Pulmonary mycobacteria infections due to *Mycobacterium avium* complex. Clinical features and course in 100 consecutive patients. Chest 1979;75:115.

[5] Rosenzweig DY. Atypical mycobacteriosis. Clin Chest Med 1980;1:273—84.

[6] Youmans GP. Tuberculosis. Philadelphia: W.B. Saunders Company; 1979.

[7] Avian Tuberculosis, In: Merck veterinary manual. 8th ed. Philadelphia: National Publishing Inc.; 1998. p. 1952.

[8] Nelson EL, Pickett MJ. The recovery of L forms of Brucella and their relation to Brucella phage. J Infect Dis 1951;89(3):226—32.

[9] Corper HC. In discussion following mutation forms of the tubercle bacillus. JAMA 1926;9(October):1210—1.

[10] Burnet F. Filamentous forms of influenza virus. Nature 1956;177(4499):130.

[11] Burnet F. Virology as an independent science. Med J Australia 1953;40(223):841—5.

[12] Xalabardar C, Formas L. Publicaciones Del Instituto Antituberculoso Francisco Moragas. 7, Barcelona; 1970. p. 1—83.

[13] Garrett L. The coming plaque. New York: Harper Collins; 1994.

[14] War Department Annual Reports (WDAR), Washington, DC: Government Printing Office; 1917. p. 346.

[15] Dubos R, Dubos J. The white plague. New Brunswick: Rutgers University Press; 1987.

[16] Grist NR. Pandemic influenza 1918. Brit Med J 1979;22(December):1632—3.

[17] Jordan E. Epidemic influenza. 1st ed.. Chicago: AMA; 1927.

[18] Flexner S, Flexner JT. William Welch and The Heroic Age of American Medicine. New York: Viking Press; 1941.

[19] Hutchinson W. The Doctor in war. Boston: Houghton, Mifflin; 1918. p. 3.

[20] Cummins SL. Tuberculosis in history. London: Bailliere, Tindall, Cox; 1949.

[21] MDWW, vol. 5. Washington, DC: Government Printing Office; 1918. pp. 486—490.

[22] Donaldson R. The bacteriology of influenza: with special reference to Pfeiffer's Bacillus. In: Crookshank, editor. Influenza. London: Heinemann; 1922. p. 139—313. 144.

[23] Shope RE, Francis Jr T. The susceptibility of swine to the virus of human influenza. J Exp Med 1936;64:791—801.

[24] Hirst GK. The agglutination of red cells by allantoic fluid of chick embryo infected with influenza virus. Science 1941;xciv:22—3.

[25] Pound A. Observation on the agglutination and haemolysis of red cells treated with extracts of *Mycobacterium tuberculosis*: an evaluation of methods. J Pathol Bacteriol 1952;64(1):131—43.

[26] Takahashi Y, Ono K. Hemagglutination reaction by the phosphatides of the tubercle bacillus. Kekkaku no Kenkyu (Tuberculosis Res) 1957;7:1.
[27] Takahashi Y, Ono K. Study on the passive hem agglutination reaction by the phosphate of *M. tuberculosis*. 1. The reaction and its specificity. Am Rev Resp Dis 1961;83(2): 381.
[28] Fontes A. Bemerkungen ueber die Tuberculoese Infection und ihr virus. Mem Instit Oswaldo Crus 1910;2: l41—6.
[29] Koch R. Die Aetiologie der Tuberculosis. Berliner Klinische Wochenscrift 1882;XIX:221—30.
[30] Nicolle C, Lebailly C. Compt Rend Acad Sci 1918;167:607.
[31] Sweany HC. Mutation forms of the tubercle bacillus. JAMA 1926;9(October):1206—11.
[32] Mellon RR, Fisher LW. New studies on the filterability of pure cultures of the tubercle group of microorganisms. J Infect Dis 1932;51:117—28.
[33] Noymer A, Garenne M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Popul Dev Rev 2000;26(3):565—81.
[34] Reid AH, Fanning G. Origin and evolution of the 1918 'Spanish' influenza virus hemagglutinin gene. Proc Natl Acad Sci USA 1999;96(4):1651—6.
[35] Reid AH, Fanning TA. Characterization of the 1918 'Spanish' Influenza virus neuraminidase gene. Proc Natl Acad Sci USA 2000;97(12):6785—90.
[36] Rhoads CP. Introduction {to a conference on viruses as causative agents in cancer}. Ann NY Acad Sci 1952;liv:872—3.
[37] van Helvoort T. History of virus research in the 20th century: the problem of conceptual continuity. Hist Sci 1994;32(2):185—235.
[38] Delbruck M (Ed.), Viruses 1950. In: Proceedings of a conference on the similarities and dissimilarities between viruses attacking animals, plants and bacteria, respectively, Pasadena, 1950.
[39] Lwoff A. The concept of virus. The third Marjory Stephenson Memorial Lecture. J Gener Microbiol 1957;xvii:239—53.
[40] Rivers TM. The nature of viruses. Physiol Rev 1932;Xii: 423—52.
[41] Klieneberger-Nobel. Filterable forms of bacteria. Bacteriol Rev 1951;xv:77—103.
[42] Iseman MD. Evolution of drug resistant tuberculosis: a tale of two species. Proc Natl Acad Sci USA 1994;91(24):28—9.

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