

The Influenza Century: 100 years of science and history writing.

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The title of my lecture tonight is *The Influenza Century*. Why the influenza century you might ask? Well, it cannot have escaped your attention that 2018 marks the centenary of the 1918 influenza pandemic – what the World Health Organization has called ‘the most deadly disease event in the history of humanity’ - and while historians like to think that they are immune to significant anniversaries, publishers’ lists suggest otherwise.

Indeed, this year has already seen three major new academic studies of the pandemic, as well several popular titles reminding us how 100 years ago the so-called Spanish flu may have been responsible for between 50 to 100 million deaths globally. After four years of programming around the First World War, the BBC has also embraced this ‘other centenary’ by commissioning a lavish new drama documentary pointing out that 10 times as many people died in the pandemic as perished on the killing fields of northern France and Flanders.¹

But it is not only in popular culture that influenza enjoys increasing visibility: in preventive health and infectious disease research circles too, flu is very much the pathogen of the moment. For example, in February, Antony Fauci, the long-serving director of the National Institutes of Health in the US, announced he was making a universal flu vaccine a strategic priority.²

With the present occupant of the White House openly hostile to science and its value to society, you could argue that this was a canny political move - after all, flu is a regular autumnal occurrence, as familiar to Americans as the fiery leaf displays that light up a New England fall; unlike Ebola or Zika, it can hardly be portrayed as a suspect foreign import.

¹ BBC2, ‘The Flu That Killed 50 million’, September 18, 2018. Available at: <https://www.bbc.co.uk/programmes/p06l5h0> (Accessed 10 October 2018).

²NIAID unveils strategic plan for developing a universal influenza vaccine (2018) National Institutes of Health (NIH). Available at: <https://www.nih.gov/news-events/news-releases/niaid-unveils-strategic-plan-developing-universal-influenza-vaccine> (Accessed: 10 October 2018).

But Fauci's announcement also reflects the inadequacy of current vaccine production technologies, which date back to the 1930s, and a recognition that, despite 100 years of scientific advances, medicine is still a long way from being able to control flu, much less predict when and where the next pandemic will strike. As Bill Gates recently reminded audiences at Davos, a 'fast moving airborne pathogen [is] the biggest public health threat the world faces in the next decade' and were there to be a repeat of a 1918-style pandemic as many as 30 million people might perish.³

I should say that Gates's figure is actually at the low end of the predicted death ranges. John Barry, the author of the *Great Influenza*, points out that, adjusting for population growth, a virus with the same mortality rate as the Spanish flu could result in between 140 million to 425 million deaths today.⁴ Those are truly staggering figures. Indeed, it is fair to say that in the 100 years since the Spanish flu emerged from an unknown animal reservoir and began spreading round the world, it has become a byword for viral Armageddon.

This present fascination with pandemic flu stands in marked contrast to the disinterest at the start of the influenza century. In 1924 the Encyclopedia Britannica didn't even mention the Spanish flu pandemic in its review of the 'most eventful years' of the 20th century. And it was a further 60 years before historians decided that the 1918 pandemic was an appropriate subject for scholarly inquiry with the publication in 1974 of Richard Collier's *The Plague of the Spanish Lady*, followed two years later by Alfred Crosby's *Epidemic and Peace* (later reissued as *America's Forgotten Pandemic*). Crosby's book, in particular, was crucial. By making influenza history writing respectable, Crosby, an environmental historian, awakened the interest of other scholars, including medical historians, and gave birth to a stream of scholarship that in 2018 shows no signs of slowing.

But *Epidemic and Peace* did not arise *de novo*. Before Crosby could become interested in influenza, flu first had to acquire a medical identity. That identity, I will

³ Bill Gates: *Infectious disease pandemic is biggest threat to humanity* - Business Insider (no date). Available at: <http://uk.businessinsider.com/pandemic-risk-to-humanity-2017-9?r=US&IR=T> (Accessed: 8 October 2017).

⁴ John Barry, 'The 1918 influenza pandemic in its time –will we learn for the future?', *Nature Research Microbiology Community*. Available at: <https://naturemicrobiologycommunity.nature.com/users/79120-john-barry/posts/29254-the-1918-influenza-pandemic-in-its-time-will-we-learn-for-the-future> (Accessed: 10 October 2018).

argue, was provided by biology, in particular the branches that comprise virology, veterinary ecology and molecular pathology. But this influence has never been only one way. Instead, in this talk I wish to suggest that our current preoccupation with flu is best understood as the product of an on-going conversation between medical science and the medical and environmental humanities. And as will all the best dialogues, it involves a back and forth, an ebb and flow.

On the one hand, virologists, ecologists and molecular pathologists have acted as important spurs to influenza history writing, particularly in the middle part of the influenza century. On the other, historians interested in questions of environmental change and cultural memory have spurred scientists to ask questions that they might not have asked otherwise *and* to devise novel tools in search of answers.

It is a dialogue in which new laboratory techniques and technologies have played a crucial role, engendering conceptual shifts in virology and making the flu virus into an important site for the production of new medical knowledge and vaccines. In the process, flu has come to occupy a key position in infectious disease research and preventive medicine, one that has seen it commanding significant research budgets and increasingly dictating institutional priorities and public health policy.

The clearest example of this came in 2009 when at the height of concerns about a severe global outbreak triggered by H1N1 swine flu, Margaret Chan, the then director general of the World Health Organization, announced a phase six pandemic alert, triggering the activation of multi-dollar contracts for pandemic vaccines.

Explaining her decision, she stated: 'The virus writes the rules and this one, like all influenza viruses, can change the rules, without rhyme or reason, at any time'.⁵ That is a statement that it would have been impossible to imagine a senior public health official making 20 years earlier, much less at the beginning of the Influenza Century.

So what happened? How exactly did the influenza virus come to make the rules and write itself into history?

'The Sphinx of epidemic diseases'

⁵ Chan, M. (2009) 'World now at start of 2009 influenza pandemic', WHO, 11 June. Available at:

http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html (Accessed 22 December 2009).

To answer that question we need to return to the 1890s and the so-called Russian influenza pandemic. Erupting in St Petersburg, the pandemic coincided with the era of telegraphic communications and was the first to be mapped by epidemiologists in real time.

Prior to the 1890s, influenza had been regarded as a suspect Italian word for epidemic catarrh. Such catarrhs visited Britain every winter and were regarded as a nuisance mainly to the elderly and those with pre-existing respiratory conditions. Although within a year Robert Koch's so-in-law Richard Pfeiffer would claim to have isolated the 'germ' of influenza – a bacterium he labelled *Bacillus influenza* – the bacteriology was disputed, leaving medics and the public unsure whether flu should be considered a true contagion or a miasmatic condition.

Moreover, while the 'excess' mortality from respiratory diseases observed during flu epidemics proved a useful way to retrospectively identify the true burden of the disease, flu epidemics were also associated with a host of vague nervous conditions. To contemporary observers this made flu difficult to pigeonhole, hence the verdict of Sir Morell Mackenzie, a leading Victorian throat expert, that influenza was 'the very Proteus of diseases, a malady which assumes so many different forms that it seems to be not one, but all diseases epitome.'⁶

This was still very much the view in 1901 when after a decade of conflicting bacteriological claims that had done little to advance faith in German laboratory methods or bring an effective prophylactic any closer, a writer for *Outlook* labelled flu 'the Sphinx of epidemic diseases.'⁷

'The thief in the night'

Although some 150,000 Britons perished in the successive waves of Russian flu, the mortality fell mainly on the elderly. This was not the case in 1918. As illustrated by this graph showing the pronounced mortality peak in adults between the ages of 20 and 40, the majority of the Spanish flu's victims were men and women of childbearing age. This W-shaped peak in midlife has never been explained.

⁶ Morell Mackenzie: 'Influenza,' *Fortnightly Review*, 49, 394 (June 1891): 877-886, p. 881.

⁷ Honigsbaum, M. (2014) *A History of the Great Influenza Pandemics: death, panic and hysteria, 1830-1920*. London: I. B. Tauris, p. 12.

Thanks to the pandemic for the first time since records began Britain's death rate exceeded its birth rate. In the US, the flu similarly reversed decades-long improvements in life expectancy. This reversal was seen as a stain on the medical profession and public health officials. In Britain Sir Arthur Newsholme, the head of the Local Government Board, had decided not to warn the public that the Spanish flu was likely to return in the autumn. Instead, he left it to local medical officers of health to recommend the best course of action.

In response to this 'failure of expertise', as Sandra Tomkins described it, in 1919 the post-war government established a new ministry to coordinate healthcare policy and appointed Newsholme's rival, George Newman, Minister of Health.⁸ Newman's first task was to file an official report examining the causes of the pandemic and the reasons for the flu's virulence. But despite commissioning leading experts to survey the scientific evidence, Newman was unable to say why the Spanish flu had proven so deadly to young adults – which was the reverse of previous flu seasons. Nor could he say where it had originated or what part, if any, war conditions had played in its spread.

Noting that the flu had proved just as deadly, if not deadlier, to populations far removed from the European theatre of war, he concluded that: 'The disease simply had its way. It came like a thief in the night and stole treasure'.⁹

Eight years later the American epidemiologist Edwin Oakes Jordan conducted a new survey and while his report raised the global death toll to 21 million, he reached a similar conclusion.¹⁰ The origin of the pandemic is 'largely shrouded in obscurity' he wrote. With so little to go on, is it any wonder historians shrugged their shoulders and instead devoted their energies to the far more compelling story of the military conflict?

Sure, whenever there was a severe recrudescence of flu, as occurred in 1927, *The Times* would bemoan the country's 'sad state of unpreparedness', but come the end of the winter flu season these concerns would fade and the pandemic would once again be forgotten.¹¹ This wasn't the case everywhere, however. Medical researchers in Britain

⁸ Sandra M. Tomkins (1992) 'The Failure of Expertise: Public Health Policy in Britain during the 1918-19 Influenza Epidemic', *Social History of Medicine*, 5(3): 435-54.

⁹ UK Ministry of Health (1920) *Report on Pandemic*. London: HMSO.

¹⁰ Jordan, E. O. (1927) *Epidemic Influenza: A Survey*. New York: American Medical Association.

¹¹ Bresalier, M. (2008) 'Neutralizing Flu: 'Immunological Devices' and the Making of a Virus Disease', in K. Kroker, J. Keelan, and P. Mazumdar (eds), *Crafting Immunity: Working Histories of Clinical Immunology*. Aldershot.

and America who had witnessed the deadly pneumonic symptoms at close quarters, never forgot their helplessness, and after the war had returned to their laboratories determined to make a new attack on the disease. Foremost among these was Walter Morley Fletcher, the head of the Medical Research Council, who had seen several colleagues die from what he called 'the black influenza' while conducting animal passage experiments in France and who, unlike Newsholme, emerged from the war with his reputation and budget enhanced.

As early as 1922, Fletcher had pledged to make the investigation of flu and other so-called 'filter-passing' pathogens a priority. To bolster his case, Fletcher pointed out that in 1918 flu had 'killed more persons in India than [had] died from the plague during the previous twenty years'. As Michael Bresalier has argued, Morley's comparison of flu and plague was way of 'forging' a new identity for virus research and modernising pathology along scientific lines.¹² However, not even Fletcher could have foreseen how spectacularly this move would succeed. Nor could he foreseen that success would come in the form of a ferret.

'The ferrets are sneezing'

By the 1930s, bacteriologists had produced vaccines against several pathogens that were too small to be seen through optical microscopes by passaging the presumed microbes through guinea pigs, mice, rabbits and macaque monkeys. But though these scientists suspected flu might also be a filter passer, efforts to demonstrate its viral aetiology were hampered by the failure to find a laboratory animal in which they could consistently reproduce the disease. And without a way of controlling and attenuating the microbe, there could be no way of making a vaccine and preventing flu.

The first clue to flu's viral identity and the wider ecology of the disease came in 1931 when Richard Shope, a Rockefeller researcher, demonstrated that an outbreak of so-called hog cholera in Iowa was actually a form of swine flu caused by a filter passing agent and that the disease closely resembled human influenza. Shope's key innovation, however, was that he was able to transfer the presumed virus to disease-free pigs simply by dropping filtered fluids into their noses.

The result was that when in 1933 ferrets at the Wellcome Laboratories in London fell ill with what was presumed to be influenza, Walter Fletcher asked Christopher

¹² Bresalier 2008.

Andrewes, Wilson Smith and Patrick Laidlaw at the National Institute of Medical Research in Hampstead to follow up. After a false start in which they inoculated the ferrets with throat washings from influenza patients, they remembered Shope's technique and dropped the filtered fluids directly into the ferrets' noses.

Within three days, Laidlaw announced "the ferrets are sneezing." Next, one of the ferrets accidentally sneezed in the face of a young research assistant, Charles Stuart-Harris, prompting him to also come down with influenza.

There could no longer be any doubt that influenza was a virus and that it was communicated in respiratory droplets. It was a significant moment, not least for Frank Macfarlane Burnet, a young Australian microbiologist and future Nobel prize winner, who was working in another part of the building perfecting a technique for cultivating viruses in hen embryos. Burnet immediately showed the technique to Wilson Smith who promptly experimented with his own secretions. The result was the cultivation in chick eggs of the first laboratory strain of influenza, named WS after Smith.

Chick-egg cultivation meant it was now possible to maintain the virus between epidemics and experiment with vaccines. By 1940, with the world once more at war, such as vaccine became a strategic priority for the military. This was especially the case in America where generals had never forgotten the devastation wrought by the Spanish flu in large Army training camps. And so it was that scientists at the Rockefeller and the NIMR in London began conducting vaccine trials in earnest.

'All influenza epidemics now are pandemics'

At the Walter Hall and Eliza Institute in Melbourne, Burnet, newly returned from London, also entered the race, assisted by William Beveridge, a young Australian veterinary pathologist who had studied the swine flu virus with Shope at the Rockefeller. Had these and other trials succeeded, the interest of historians might have been awakened sooner. But the results were inconclusive and with no major epidemic or pandemic in sight, the war once again had the best narrative lines. However, this wartime work brought new immunological insights – insights that would become increasingly important in the second half of the influenza century.

After isolating his own Melbourne strain of the virus, Burnet studied its adaptation in mice, a far more amenable experimental animal than ferrets. In the process he established that there were two types of flu, A and B, and elucidated the crucial role that

proteins on the surface of the flu virus played in pathogen virulence and shifting morbidity and mortality patterns.

Indeed, when Burnet compared notes with colleagues in England and North America, he realised that new flu strains typically appeared first in Australia in June, during the southern hemisphere winter, with the same variant being responsible for outbreaks in the northern hemisphere six months later – a phenomenon Burnet called ‘immunological drift’. These variants were subsequently distinguished by their ability to agglutinate in the presence of haemoglobin, leading to their classification as H1, H2, H3, etc.

It was the beginning of the recognition that flu viruses continually circulate between the two hemispheres and that from an epidemiologic point of view the world was a single immunological unit. Or as Burnet put it in 1953, “all influenza epidemics nowadays are pandemics.”¹³

Ladies and gentleman, we are almost at the midpoint of the influenza century. Until now, influenza has been of interest to few people outside of medical research circles. But with the recognition that epidemics and pandemics are determined by changes to proteins in the flu virus and that by monitoring these antigen changes it may possible to manufacture preventive vaccines, flu entered a new era – the era of pandemic preparedness. Indeed, by the 1950s the WHO had established a network of 85 reporting laboratories for surveilling flu and was monitoring these antigenic changes on a regular basis. But this new surveillance technology came at a cost: for what if the vaccines proved a poor match for or could not be manufactured in time? What, in short, if the virus *had its way*? Would the result be a repeat of 1918?

‘Can it happen again?’

The first writer to recognise the implications of this anxious new reality was a journalist, Charles Graves. Charles’s mother had died of Spanish flu in July 1918 and his brother, the novelist Robert Graves had contracted the disease in February 1919 while on his way back to the family home in Wimbledon to collect his demobilization papers, so Charles had a personal reason for following the latest scientific developments.

¹³ Burnet, M. (1953) *Natural History of Infectious Diseases*. Cambridge University Press, p. 287.

The immediate impetus, however, was an outbreak in the Far East in May 1957. That outbreak was quickly labelled 'Mao Flu' by the tabloid press and by June these same newspapers were reporting that a quarter of a million people had been hospitalized in Hong Kong. As virus samples were flown to London in the hope of manufacturing a vaccine, Graves decided to revisit the 1918 pandemic and ask "Can it happen again?"

Today, such questions have become routine. It is not *if* there will be a new pandemic, we're constantly told, but *when*. But in 1957 they were not routine and, fearing it might be accused of "frightening the public" should the feared pandemic fail to emerge, Graves's publisher hesitated. The result was that it was not until after the subsequent 1968 pandemic that Graves's book finally went on sale.¹⁴

"At last, on the 50th anniversary of the greatest plague in history, comes the first world-wide account of the so-called Spanish flu, [the victims of which far outnumbered the Black Death itself]," declared the book jacket. Inside, Graves drove home the message by informing readers that though the 1957 and 1968 pandemics had been mild compared to 1918, "there is no reason why a really virulent outbreak should not occur at some later date."¹⁵

'The field has been well and truly tilled'

Graves was not the only journalist who had been paying attention to these new virological insights. In 1974 Richard Collier, who had been an editor on Mountbatten's *Phoenix Magazine*, became the second writer to revisit the 1918 pandemic. To aid his research, he approached prominent flu experts to read his manuscript and give advice. One of these was Charles Stuart-Harris, the co-discoverer of the flu virus. "I am interested to know that you are writing a book concerning the grisly affair of 1918/19," he grandly informed Collier in 1973. "I am not familiar with your sort of research but the field has been well and truly tilled."¹⁶

Stuart-Harris's response is revealing. After leaving the NIMR, Stuart-Harris had become the first professor of medicine at Sheffield University. There he had conducted polio vaccine trials and researched the common cold. His assumption almost certainly

¹⁴ Graves, C. (1969) *Invasion by Virus: can it happen again?* London: Icon.

¹⁵ Graves (1969), p. 9.

¹⁶ I am grateful to Hannah Mawdsley for drawing my attention to Stuart-Harris's comment and for her permission to reproduce it here.

reflected a widely held medical view at the time: after all, what more could Collier possibly say that hadn't already been better said by him or Burnet?

But Stuart-Harris was wrong. Drawing on the personal testimonies of 1700 flu survivors, Collier, who had previously written books on Dunkirk and Mussolini, was the first to tap into cultural memories of the pandemic and capture the spreading panic as the virus circumnavigated the globe. In his appendix, Collier even provided a summary of the science.

Flu, he explained, was “a quick change artist” that was “forever rearranging its proteins.” The problem was this process was not well understood, so it was “still possible that a pandemic virus might return and kill ... millions.” Collier even parsed the latest ecological theories by explaining that some scientists suspected pandemic viruses could lay hidden in animal reservoirs, such as pigs, chickens and ducks, before concluding: “This threat makes the continual watch for new variants as necessary now as at any time in the past.”

Epidemic and Peace, aka ‘America’s forgotten pandemic’

Until now I have said little about immunology but in 1976 another book appeared, one that was to set the benchmark for all subsequent histories. Alfred Crosby claimed the genesis for *Epidemic and Peace* came in the early 1970s when he was browsing an almanac and on a whim looked up the table for US life expectancy.¹⁷ In 1917 and 1919 it had been 51 years but in 1918 it had fallen to 39 years, prompting Crosby to ask, “What the hell happened?”¹⁸ The answer, of course, was the Spanish flu happened. Crosby, then a researcher at Washington State University, promptly applied for a grant from the National Institutes of Health, and set about transforming himself into a world expert.

Crosby’s main historiographical contribution was to claim that, despite its neglect by military and political historians, the flu had had a demonstrable effect on world affairs. In particular, he argued that Woodrow Wilson’s illness from flu during the Versailles peace negotiations in Paris in April 1919 had caused the American delegation to accede to French demands for harsher German reparation payments, thereby sowing the seeds for the collapse of the Weimar Republic and the rise of Nazism in the 1930s.

¹⁷ Crosby, A. W. (1976) *Epidemic and Peace, 1918*. Westport, CT: Greenwood Press.

¹⁸ Kolata, G. (1999) *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It*. New York: Farrar, Straus and Giroux, p. 8.

The other widely cited chapter was Crosby's 'Afterword' in which, noting the curious absence of references to Spanish flu in the writings of American novelists and politicians who had lived through the pandemic, he suggested the virus's impacts had been expunged from cultural memory, hence his rebranding of the pandemic in 1989 as "America's forgotten pandemic."¹⁹

Just as remarkable, however, is the way that Crosby drew on the latest scientific insights to explore the flu's unusual virulence and the variations in death rates observed between cities and rural areas, and remote island communities. Indeed, Crosby's book can be seen as much as an epidemiological and virological detective story as an inquiry into the vagaries of cultural memory.

Thus while in America and Europe the average mortality rate was 3 percent, he observed that in Alaska and Western Samoa the virus has behaved as a "virgin soil" infection wiping out half the indigenous populations. In this respect, he argued, Spanish flu was comparable to other great scourges from the past, such as the Black Death, which killed an estimated 40-70 Europeans in the middle decades of the 14th century, or the epidemics of measles and smallpox that wiped out Amerindian populations following the discovery and settlement of the Americas by European colonists in the early 16th century – a theme Crosby had already explored in his seminal writings on the "Colombian exchange."²⁰

Like William H. McNeill, whose *Plagues and Peoples* was also published in 1976, Crosby's insights were based on a synthesis of the latest ecological and immunological thinking. A key influence was Burnet's 1945 Dunham Lectures at Harvard, later published as *Virus as Organism*, in which he urged epidemiologists to regard virulence not simply as a property of pathogenic microorganisms but in ecological terms as "interactions" between hosts and parasites.²¹ Over the long term, such interactions favoured balanced, avirulent infections without disease, Burnet argued. By contrast, when a pathogen adapted to one species suddenly invaded a new host – as occurred with human infections

¹⁹ Crosby, A. W. (1989) *America's Forgotten Pandemic: The Influenza of 1918*. Cambridge; New York: Cambridge University Press.

²⁰ Crosby, A. W. (2003) *The Columbian Exchange: Biological and Cultural Consequences of 1492*. Westport, CT.: Greenwood Publishing Group.

²¹ Burnet, M. (1945) *Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases*. Cambridge, MA: Harvard University Press, p. 28

triggered by zoonotic diseases such as psittacosis - epidemics and pandemics were to be expected.

In 1976 Crosby did not have the evidence to support this reading of the flu pandemic – by the 1970s, wild influenza viruses had been isolated from shearwaters and other migratory birds, but scientists had yet to connect ducks and chickens to human outbreaks. Nonetheless, he clearly recognised the importance of Burnet’s immunological insights, hence his conclusion that the Spanish flu’s deadliness lay in “a balance between two factors each of which defines the other... the virus’s virulence and the hosts’ vulnerability.”²²

In the course of researching his book, Crosby also came across an intriguing report in the *Washington Post* in 1951. It concerned an expedition to Alaska led by a young Swedish pathologist, Johan Hultin. Together with his academic supervisor, Hultin had travelled to a remote Inuit village in the Seward peninsula of Alaska that had seen half its population wiped out by the flu. Once there, he had excavated the bodies of victims buried in the permafrost in search of genetic fragments from the virus. Unfortunately, in 1951 laboratory techniques were not sufficiently developed to enable the recovery of viral RNA, leading Crosby to conclude: “It has been the dream of scientists working on influenza for over a half century to somehow obtain specimens of the virus of Spanish influenza, but only something as unlikely as a time capsule could provide them.”

It was a rare example of Crosby’s faith in science failing him.

A time capsule called ‘Lucy’

Crosby’s book, which won the American Medical Association’s 1976 award for the best book on a medical subject, was hugely influential. Suddenly, influenza was a respectable subject for scholarly inquiry and academic publishers were soon besieged with proposals for monographs by newly qualified PhDs. Coinciding with the 1976 scare over an outbreak of swine flu at an American army base in New Jersey, Crosby’s book also triggered the interest of military historians, such as Caroline Byerly, a researcher in Office of the Surgeon General.

The result was *Fever of War* in which Byerly explored the role that America’s entry into the WW1 may have played in the amplification and spread of the pandemic virus. In particular, drawing on the theories of the evolutionary biologist Paul Ewald, Byerly

²² Crosby (1976), p. 306.

hypothesized that trench warfare and crowded Army barracks may have provided the ideal epidemiological and evolutionary conditions for the emergence of a virulent mutant adapted to young adults by ‘continuously bringing the virus into contact with new hosts - young healthy soldiers.’²³

The AIDS pandemic also renewed popular interest in the 1918 flu, hence Cambridge University Press’s decision to reissue Crosby’s book in 1989 with its revised title. However, the events that more than any other fired the second wave of flu scholarship was the 1997 outbreak of bird flu in Hong Kong and the publication the same year of the initial sequence of the Spanish flu virus by a young molecular pathologist based at the Armed Forces Institute of Pathology (AFIP) in Bethesda, Maryland. In 1995 Jeffrey Taubenberger and his colleague, Ann Reid, developed a technique for extracting fragile viral genetic material from damaged or decayed tissue. Soon after, Taubenberger read how researchers had used another new technique, polymerase chain reaction or PCR, to isolate the genes for colour blindness from the preserved eyeballs of a famous chemist, John Dalton. What, he wondered, if he were able to solve other medical puzzles using PCR and the extraction techniques he and Reid had pioneered at the AFIP?²⁴

Taubenberger immediately held a brainstorming session where it was pointed out that among the AFIP’s three million pathology specimens were autopsy samples taken from US soldiers in 1918. What if some of the preserved lung tissue contained fragments of the Spanish flu virus? Might it be possible to fish them out and sequence the genome?

After an agonizing year of negative results, Taubenberger got his answer. In 1996 he isolated an influenza-positive sample from a soldier who had died in September 1918 at Fort Jackson, South Carolina. But while Taubenberger was able to sequence four of the eight genes of the 1918 flu virus there wasn’t sufficient material to complete the analysis. Nevertheless, in March 1997 Taubenberger published his findings in *Science*.

According to John Oxford, a British virologist who had studied with Charles Stuart-Harris and had long harboured a similar ambition, Taubenberger’s paper ‘was like a star appearing in the firmament’ and catapulted the unknown flu researcher onto the front

²³Byerly, C. (2005) *Fever of War: The Influenza Epidemic in the U.S. Army during World War I*. New York: New York University Press, p. 93.

²⁴ Interview with author, National Institutes for Health, Bethesda, MD. 22 February 2018. See also, Episode 2. ‘Resurrecting the Killer’, *Going Viral: The Mother of All Pandemics*. Available at: <https://directory.libsyn.com/shows/view/id/123829> (accessed 6 February 2019)

pages of newspapers worldwide.²⁵ More importantly, it also alerted Johan Hultin, who had never given up his own ambition to retrieve virus from the permafrost, that science had finally caught up with history.

To cut a long story short, Hultin returned to the Seward peninsula and with the agreement of village elders excavated the body of an obese Inuit woman who had been buried on a bluff overlooking the beach. After taking samples of her frozen lung tissue, Hultin bagged them and sent them to Taubenberger. Together with another pathology specimen from the AFIP archives, the material from 'Lucy', as the woman was dubbed, enabled Taubengerger to complete the genetic sequence. He had found Crosby's time capsule.

The complete sequence was finally published in 2005 and it contained a surprise. All but five of the molecules of the H1N1 virus matched sequences from wild birds, or as Taubenberger told *Nature*: 'It is the most bird-like of all mammalian flu viruses.' Using a technique called plasmid-based reverse genetics, other researchers at the US Centers for Disease Control and Prevention then made new copies of the virus and infected mice and ferrets to test its virulence. Unlike modern human flu viruses, which cause limited viral replication and disease in mice, the 1918 virus was lethal, killing the mice and ferrets in three days.

Combined with the news that a hitherto obscure strain of avian influenza, known as H5N1, which had first emerged in Hong Kong in 1997, was now causing isolated human outbreaks across Southeast Asia, these studies raised the spectre that the next pandemic was just around the corner and history might be about to repeat itself. Thus it was that flu science gave birth to a new pandemic panic and a new wave of popular titles such as Pete Davis's *Catching Cold*, John Barry's *The Great Influenza*, and Mike Davis's *The Monster at the Door*.

'I had a little bird/It's name was Enza'

Medical historians were slower off the mark but by time of the 90th anniversary of the pandemic in 2008, new academic titles were also rolling off the presses, including my

²⁵ Interview with author 7 November 2017. See also, Episode 1. 'Bringing Up The Bodies', *Going Viral: The Mother of All Pandemics*. Available at: <https://directory.libsyn.com/shows/view/id/123829> (accessed 6 February 2019)

own book, *Living With Enza*, named for a playground rhyme about the flu.²⁶ As is clear from my subtitle – ‘The Forgotten Story of Britain and the Great Flu Pandemic’ - the book owed a clear debt to Crosby, showing how it was not only in America that the pandemic had been erased from cultural memory.

However, the genesis of *Living With Enza* dates back to 2005 when *The Observer* newspaper sent me to Vietnam to write about an outbreak of avian influenza. There, I had the opportunity to interview scientists like Robert Webster, the so-called ‘Pope of bird flu’, and Jeremy Farrar, the director of the Wellcome Trust but then a young clinician based in Saigon who had just documented the death of a young girl from an H5N1 virus acquired from her pet duck. Later, I also got to know John Oxford who fired my imagination with his theory that the pandemic had started at a British military camp at Etaples in northern France not far from the Somme estuary, a well-known bird migratory ground.²⁷

For more on this and the rival American and Chinese origin theories, I point you to Laura Spinney’s *Pale Rider*, which was published last year just in time for the centenary.²⁸ Or you could listen to my podcast series, *Going Viral: The Mother of all Pandemics*, in which I interview Oxford and Taubenberger and discuss the latest scientific theories about why young adults were so vulnerable to the Spanish flu. One of those theories, known as ‘original antigenic sin’, is worth a book on its own.²⁹

In conclusion, for all the C.P. Snow-like talk of a divide between science and the humanities, when it comes to influenza history writing it seems to me that the two cultures distinction evaporates. This is not only the case for medical historians. Talking to Oxford, who writes poetry in his spare time, and to Taubenberger, who composes sonatas for clarinet and cello, I was struck by their deep interest in the cultural and social history of the pandemic and their respect for professional historians. Indeed, when he succeeded

²⁶ Honigsbaum, M. (2008) *Living With Enza: The Forgotten Story of Britain and the Great Flu Pandemic of 1918*. Basingstoke; New York: Palgrave Macmillan.

²⁷ In March 2018, John and I visited Etaples to record an episode of my podcast, *Going Viral: The Mother of All Pandemics*. Available at : <http://goingviralthepod.libsyn.com/>

²⁸ Spinney L. (2017) *Pale rider: the Spanish flu of 1918 and how it changed the world*. London: Jonathan Cape.

²⁹ Honigbaum, M. and Mawdsley. H. (2018) *Going Viral: The Mother of all Pandemics*. Available at : <http://goingviralthepod.libsyn.com/>

in sequencing the flu's genome, one of the first people Taubenberger contacted was Crosby to tell him: 'I've found the time capsule.'³⁰

Unfortunately, Crosby died in March 2018 , almost 100 years to the day of the first documented outbreak of a pandemic-like illness at Camp Funston, Kansas. Whether or not that outbreak *was* Spanish flu is a question that, at time of writing, science has been unable to answer – the earliest physical isolates of the pandemic virus from a US Army camp date from May 1918 and there are several reasons to doubt the Kansas-origin theory.³¹ But only a fool would bet against another time capsule emerging at some point in the future. And when it does, it would be surprising if it did not act as a spur to another history of the Spanish flu.

Thank you.

³⁰ Interview with author, National Institutes for Health, Bethesda, MD. 22 February 2018.

³¹ For a recent review of the various origin theories see: Worobey, M., Cox, J. and Gill, D. (2019) 'The origins of the Great Pandemic', *Evolution, Medicine, and Public Health*. Available at: <https://doi.org/10.1093/emph/eoz001>