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THE GREAT INFLUENZA EPIDEMIC OF 1918-9

And the Virus that Caused It

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Summary

The influenza epidemic of 1918-19 was the deadliest in history. It killed more people in a year than the Black Death plague of the Middle Ages did in a century. The cause of influenza was not known at that time and no specific treatment was available. Supportive care, attempts to halt the spread of the disease by isolation, quarantine, the closure of public gatherings, the promotion of personal hygiene, and the wearing of masks were somewhat helpful in reducing the death rate from the disease. The second wave of the epidemic, between September and December 1918 caused more than half of deaths and was unusually deadly for young adults. The virus causing influenza was not isolated until the 1930's. The specific influenza virus causing the 1918-9 pandemic was unknown until the 1990's when scientists at the Armed Forces Institute of Pathology developed techniques for obtaining molecular assays from autopsy material. That the 1918 virus was of the H1N1 type was confirmed by examination of material obtained from a corpse dug from the permafrost in Alaska. Subsequently the extinct 1918 virus was reconstructed and thus available for study. Another influenza pandemic is inevitable, for which we are not adequately prepared. Particularly important is the development of a "universal" influenza vaccine. Better antiviral agents are also needed. Adequate global comprehensive pandemic preparedness and response plans are essential, but have not yet been developed.

Background of the Author

Boyd A. Nies was born and raised in Orange, California. He graduated from Stanford University in 1956 and from the Stanford University School of Medicine in 1959. An internship and residency in internal medicine at the UCLA Medical Center and the Wadsworth Veterans Administration Hospital was followed by sub-specialty training in hematology and medical oncology at the National Cancer Institute in Bethesda, Maryland and the Stanford University Medical Center. From 1965 to 1995, he practiced hematology and medical oncology in Redlands and San Bernardino. During periods of that time, he was Chief of the Medical Staff of St. Bernardine Hospital and was also on the clinical faculty of the UCLA Medical Center. After retirement from full-time practice, he was the Medical Director of the St. Bernardine Hospice for 2 years and later served as a medical oncology consultant for a technology company. During retirement he has been a board member, and has also served as president, of the Watchorn Lincoln Memorial Association, the Friends of A. K. Smiley Public Library, and Lifestream (formerly the Blood Bank of San Bernardino and Riverside Counties). He has been married to the former Helen Salter for 61 years. They have 3 children and 6 grandchildren. This is Boyd's sixth Fortnightly paper.

THE GREAT INFLUENZA EPIDEMIC OF 1918-9

AND THE VIRUS THAT CAUSED IT

Now largely forgotten except as a footnote to World War I, the 1918-19 influenza pandemic was, in fact, one of the worst catastrophes in human history. Of the world's total population of about 1.8 billion in 1918, the latest comprehensive accounting of influenza's global mortality indicates that at least 50,000,000 died. However, even this astounding number may have been an under estimate, due to the lack of information from vast areas of the world. In any case, the deaths from the pandemic vastly exceeded the combined military and civilian deaths during World War I, estimated at about 17 million. Only in Europe did deaths from the War exceed those from influenza. The United States had a relatively low death rate from the epidemic, but still lost 675,000 to influenza compared to about 116,000 killed in the War. The death rate was much higher in Asia, particularly in areas where malnutrition and lack of medical care were widespread. In Western Samoa more than 20% died. Mortality was 25-50% in Alaskan natives. Another measure of the influenza devastation: More died in the influenza pandemic than have died thus far from AIDS.

The epidemic was known as the "Spanish flu". In May 1918, King Alfonso XIII, along with his prime minister and members of his cabinet, fell ill with influenza. Although the disease had already been present in the U.S. and France by then, that news had been was suppressed in other areas of Europe. The British, French and American governments may have encouraged adoption of the "Spanish Flu" name, although it is now clear that the disease neither started in Spain, nor was it worse there than in other areas of Europe.

The pandemic is generally considered to have taken place in three waves. The first wave, in the spring and summer of 1918, was relatively mild in terms of mortality, similar to the seasonal flu, which we experience yearly. The second wave, between September and December 1918, was much more severe and was associated with most of the deaths. The third wave in 1919 was intermediate in severity.

There was some variation in the wave pattern between countries. In Australia, there was single more prolonged wave of activity in 1919, the

disease having been delayed due to a previous partially successful marine quarantine. In Scandinavia and in a few other places, the disease persisted into 1920.

The earliest known cases occurred in Haskell County, which is in western Kansas, and this may be where the pandemic started. In this scenario, an army inductee from western Kansas carried the virus to Camp Funston on the grounds of Ft. Riley in Manhattan, Kansas. A cook there developed influenza in March 1918. Barracks and tents were overcrowded and inadequately heated. Within three weeks, 1100 soldiers were admitted to the hospital with that disease. Soldiers from Camp Funston were sent to other bases in the United States and overseas to Europe further spreading the disease.

Other authorities have suggested that the epidemic started in China. Many pandemics do start in Asia, probably because many people there have close contact with birds and animals. Although China was officially neutral in World War I, its government in cooperation with France and Britain created the Chinese Labor Corps, largely in secret. Men in the CLC did not take part in combat, but provided support services such as digging trenches, assembling shells and repairing equipment. The approximately 135,000 sent to Europe traveled both westward through Canada and also eastward around the Cape of Good Hope. There is some evidence that a respiratory illness developed while thousands were crammed into a station at the Canadian entry point on Vancouver Island. The CLC guards were exposed and may have passed on the illness to the civilian population. The men were subsequently herded into sealed guarded trains and sent cross-country, from which they sailed to Europe.

A British virologist, John Oxford, proposed a third origin theory. A respiratory illness broke out in a vast Allied camp in northern France in the winter of 1916-17. It was called “purulent bronchitis”. Autopsies on some of the patients who died there showed changes similar to those subsequently noted in the Spanish flu.

It is likely that we will never know, for sure, where the great pandemic started, but it did not start in Spain.

Scientific medicine was becoming well established in Europe and the United States by the beginning of World War I. In the late 19th century, Louis

Pasteur in France and Robert Koch in Germany established that many infections were due to bacteria. Techniques were developed so that bacteria could be cultured from diseased secretions and tissues and specifically identified. In 1892, during an influenza epidemic in Europe, Richard Pfeiffer, a German physician and bacteriologist, found a bacterium in the sputum of many affected patients, which he believed was the cause the disease. He named the organism Bacillus influenzae, which today we know as Haemophilus influenzae. Pfeiffer's bacillus, as it was commonly known, was accepted by many scientists and physicians as the cause of influenza for many years. Viruses were unknown at that time, although it had been shown by the Russian botanist Dmitri Ivanovsky in 1892 that an infectious agent small enough to pass through unglazed porcelain caused a disease in tobacco plants.

Successful treatments against tetanus and diphtheria were developed. The organisms causing those diseases produce a toxin, which when injected into horses elicits an immune response producing antibodies against the toxin. The harvested horse serum can then be used to treat patients with those diseases.

Johns Hopkins medical school, the first American medical school of the scientific German type, opened in 1893. At that time, only a handful of medical schools required a college education. Some medical schools, in fact, had no education requirements, and their graduates received no laboratory training, did not dissect cadavers, and in some cases saw no patients. The Flexner medical report on medical education in 1910 concluded that 120 of the about 150 medical schools in existence at that time should be closed. Many were closed and others remained open only after having been taken over by universities. The Rockefeller Institute was established in 1901 and became an important center for medical research.

Despite these advances in medicine and medical education, physicians had almost no tools to prevent or treat the coming epidemic of influenza and associated pneumonia. Vaccines incorporating Pfeiffer's bacillus were ineffective. A serum, containing antibodies against strains of the pneumococcus, showed some effectiveness against that organism, but was not readily available. Viruses had not yet been discovered, so there were no diagnostic tests. There were no effective anti viral agents or antibiotics. Supportive care and attempts to halt the spread of the disease by isolation,

quarantine, closure of public gatherings, the promotion of personal hygiene, and the wearing of masks were all that could be done.

The disease spread rapidly. By April 1918 it was widespread in cities of the east where soldiers embarked and shortly thereafter in the war zones in Europe. By May, it was reported successively in Eastern Europe, Southern Russia, China and Japan. Crowding and massive troop movements contributed to the spread of illness to hundreds of thousands of soldiers on both sides. Although the death rate was relatively low in those months, military operations were greatly affected.

Russia's participation in the War ended with the signing of the treaty of Brest-Litovsk in March 1918. German troops, previously in Russia, became available for use on the Western Front. The German commander Eric von Ludendorff then began a massive campaign on the Western Front before American participation was at a high point, which he felt was Germany's last real chance to win the War. Initially the offensive produced huge gains, the Allies being pushed back over 60 kilometers. A second phase was started in early April and again produced further gains. In mid April, however, the flu began to hit the troops on both sides. There is some evidence that the Germans were more severely affected, probably worsened by inadequate rations. The third phase of the offensive was delayed and when finally begun in late May faltered and then failed. Subsequently, Allied counter attacks drove the Germans out of France. Ludendorff blamed influenza for the failure of the operation and the loss of the War. Whether this was indeed true is a matter of speculation, although many historians do agree that the flu hastened the end of the War.

Cases of influenza seemed to be diminishing during the summer of 1918 and on August 10, the British high command proclaimed the end of the epidemic. Within days of this proclamation, however, the disease returned in a far more deadly form. This second wave was initially reported in Brest in France, Freetown in Sierra Leone, and in Boston. Brest was the landing port for nearly 40% of the American Expeditionary Forces and also was a training site for French naval troops. The disease may have arrived there from either of those two groups. Freetown was a major coaling port on the west side of Africa. A British naval ship may have brought it there. Probably a ship from Europe brought the disease to Boston. Over the next two months the disease spread to nearly every part of the earth.

In Boston, at the Commonwealth Pier, the Navy operated a barracks, usually overcrowded, for up to 7000 sailors in transit. 35 miles away, north west of Boston, was Camp Devens. It is not entirely clear whether the disease spread from the naval facility to the camp or, whether it developed independently at the two sites, or even whether it spread from the camp to Boston. Camp Devens was an army camp built to hold a maximum of 36,000 men. It had a hospital which could accommodate up to 1200 patients. In early September 1918, there were 45,000 men at Camp Devens, but there were only 84 patients in the hospital. Over the next two weeks the disease exploded. By September 22, almost 20% of the entire camp was ill, most of whom were hospitalized. Eventually, the hospital was filled with more than 6,000 men. Beds were placed in every available space. By that time, the medical and nursing staff itself was decimated. Bed linens soiled with blood, urine, and feces were not being replaced. A horrible stench filled the hospital. Corpses were stacked like wood near the morgue.

Dr. Roy Grist, one of the army physicians at the hospital described the illness (as quoted in John Barry's book): "These men start with what appears to be an ordinary attack of LaGrippe or influenza, and when brought to the hospital they rapidly develop the most vicious type of pneumonia that is ever been seen. Two hours after admission they have mahogany spots over the cheekbones, and a few hours later you can begin to see the cyanosis extending from their ears and spreading over their face, until it is hard to distinguish the colored man from the white. It is only a matter of a few hours until death comes…. It is horrible. One can stand it to see one, two or 20 men die, but to see these poor devils dropping like flies…. We have been averaging 100 deaths per day…. Pneumonia means in about all cases death…. We have lost an outrageous number of nurses and doctors, and the little town of Ayer is a site. It takes special trains to carry away the dead. For several days there were no coffins and the bodies piled up something fierce…. It beats any site they ever had in France after a battle. An extra long barracks has been vacated for the use of the morgue and it would make any man sit up and take notice to walk down the long lines of dead soldiers all dressed and laid out in double rows…. Goodbye old pal, God be with you till we meet again."

On September 7, 1918, sailors were sent from Boston to the Philadelphia Naval Yard. A few days later days later influenza broke out there and subsequently spread to the city of Philadelphia. The director of the Philadelphia Department of Public Health and Charities, Dr. William

Krusen, a political appointee, initially denied that an epidemic was in progress. He ignored the advice of several doctors and allowed a Liberty Loan parade, which would raise millions for the war effort, to go ahead on September 28. This parade was the largest in the city's history. Several hundred thousand gathered to watch this two-mile long parade which featured multiple bands, Boy Scouts, women's groups, and many military personnel. Within 72 hours, all of the city's hospitals were completely filled. On October 5, Krusen banned all public meetings in the city including churches, theaters, schools, and further Liberty Loan gatherings, but it was too late. The death rate per day went from a few to several hundred in the next few days. The dead bodies could not be properly disposed of. 200 corpses were stacked up at the city morgue. Others were left in place in homes. Undertakers were overwhelmed. Gravediggers were either ill or refused to bury the bodies. A plan to have prisoners dig graves was considered, but could not be carried out because there were no available guards to watch them. The disease finally peaked in mid October, with 4,597 people dying of influenza in the week ending October 16. Then, surprisingly, new cases fell precipitously, so that by November 11 the disease had practically disappeared.

In New York City, the public health commissioner was Royal S. Copeland, the dean of a homeopathic medical school, also a political appointee. When influenza appeared in September he initially took no action. When it became obvious that there was an epidemic, he took a number of measures, which resulted in New York City having the lowest death rate per population of any city on the East coast. He staggered the opening times of shops, schools and factories, thereby eliminating rush hour. Public Heath information was distributed city wide by the press, which was particularly important for the many poor Italian immigrants living in crowded tenements. He insisted that patients who lived in shared accommodations be hospitalized. Additional health centers were established. Surprisingly, children were allowed to go to school, since children after infancy seemed to be relatively unaffected by the disease, but were not allowed to attend theaters. This turned out to be a good policy, with the schools also being helpful in disseminating public health information. Despite all these measures, there were many deaths in New York as well. Copeland estimated that the epidemic had made orphans of 21,000 children.

In 1918, the population of Los Angeles was about 500,000. This was about a third of Philadelphia's population and about a tenth of New York's. The first

cases of influenza in Los Angeles were noted in mid September in sailors abroad a naval vessel which had docked in the harbor. The first civilian cases appeared on September 22. The City Health Commissioner Dr. Luther Milton Powers and Mayor Frederic Thomas Woodman worked together to craft a plan to limit the coming epidemic. A Medical Advisory Board consisting of 11 prominent physicians was appointed. This group joined by prominent civic leaders recommended closing schools, theaters, churches, dance halls, and other public meeting places. A state of emergency was declared and Dr. Powers was given the authority by the City Council to carry out those recommendations. An upcoming Liberty Day Parade was cancelled. Despite challenges particularly from the Christian Science Church and the theater owners, the bans remained largely in place until the epidemic subsided in early 1919. As a result of those measures, Los Angeles experienced a relatively low epidemic death rate of 494 per 100,000 people. San Francisco, which reacted slowly to the disease, had a rate of 673 per 100,000.

In early October 1918, a severe epidemic of "grippe" broke out in Bekins Hall, the women's dormitory at the University of Redlands. Because of this illness, the University was closed on October 7, and remained so for two weeks. A week later, the city trustees issued an order closing all schools, movie theaters, and churches and prohibiting public gatherings of any kind. The scheduled speech by Governor William D. Stephens in support of the Liberty Loan was cancelled. By early November, the epidemic appeared to be waning in the civilian population. On November 4, the public schools were reopened and two days later midweek church services were held at the Methodist and Presbyterian churches, with the other churches resuming their services on the following Sunday. However, despite the ebbing of influenza in the community as a whole, the epidemic again struck the University, this time primarily men, particularly those in the Student Officers Training Program. The University was then closed a second time. The civilian death rate in Redlands was low, probably in part due to the aggressive measures taken by the City and the University. The city physician, Dr. William A. Tatavall reported in the Redlands Daily Facts of January 14, 1919 that the influenza epidemic had been mild in Redlands. Of the more that 2000 cases, there were only 19 deaths. A recent review of burial records from Hillside Cemetery for the first six months of 1919, looking for influenza and pneumonia related deaths, found 20 such records, but only 12 were of residents of Redlands at the time of death. Adding these 12 to the previously

reported 19, gives an epidemic death rate of 310 per 100,000 population, far below that in Los Angeles. (This assumes a Redlands population of 10,000.)

Despite the success of isolation and quarantine in the civilian sector, these measures were often not instituted by the military authorities. Many of the soldiers who died in World War I were killed by influenza rather than battle wounds. For example, of the 40 Redlanders in the Armed Forces who died during the War, 12 died of influenza or pneumonia.

Immediately after a medical team visited Camp Devens, it's chairman, Dr. William Welch, Dean of the Johns Hopkins School of Medicine, called the U.S. Surgeon General William Gorgas's office urging that all transfers of troops be frozen unless absolutely necessary and that under no circumstances should transfers from infected camps be made. These recommendations were passed on to the military authorities, but were initially essentially ignored. Troops were needed in Europe and troopships continued to carry thousands to Europe, often without adequate precautions. What happened on the Leviathan, is illustrative of the problems caused by influenza on many other troopships. The Leviathan was the largest and one of the fastest ships in the world. Previously known as the Vaterland, she had been the pride of the German navy. At the start of the War, she had been anchored in New York harbor, and was subsequently seized undamaged by the U.S. navy when America entered the War. The Leviathan sailed from Hoboken, New Jersey for France on September 29 with 9,000 troops and crew aboard. Medical authorities warned against sending troops from camps known to be infected or exposed to the disease, urged a quarantining of troops going overseas for one week before departure, and warned about overcrowding. These recommendations were ignored, although the army did not allow obviously infected troops to board and planned to quarantine those who developed influenza en route. As could have been expected, the flu broke out 48 hours into the trip. Sick bay was quickly overwhelmed. The infected took over other areas of the ship and many were placed on deck. Conditions were described as horrific. Blood and vomit covered the floors and were tracked through out the ship by the healthy. Massive overcrowding overwhelmed the ventilation systems, producing a terrible stench. Groans and cries for help were heard throughout the ship. The nurses and doctors on board, many of whom became ill themselves, did the best they could, but could not attend all those who needed treatment. By the time the ship docked at Brest, 2,000 were ill and about 90 had died. Similar stories played out on other "death" ships. Fortunately, the War ended in November, so that

massive troop transports to Europe were no longer needed. Lives were also saved by Provost Marshal Crowder who, on September 26, cancelled the following two draft calls, believing that adequate training was impossible under the then current conditions.

The second wave of the epidemic was unusual on a number of counts. The disease was very severe, the death rate was high particularly among young adults, and the progression of symptoms in some cases was very rapid. The Journal of the American Medical Association reported such a case: "One robust person showed the first symptoms at 4:00 pm and died by 10 am." In Cape Town, South Africa, a man boarded a streetcar for a 3 mile trip home, during which the conductor and 6 other people died of the flu. In most influenza epidemics, the highest death rates are in the very young and very old. When mortality rates are plotted, a U shaped curve is obtained. In the 1918 pandemic, the high death rate in the 20 to 40 age group produced a "W" shaped curve. The reason for this phenomenon is unknown. Some have speculated that the elderly may have been relatively protected by their exposure to the 1889-90 epidemic, whereas the younger group was not. Others have postulated that a robust disordered inflammatory response in these otherwise healthy younger individuals may have been a contributing factor. Pathologic changes in the lungs of many of those patients were consistent with that hypothesis, showing necrosis of the lining of the bronchial tree with massive exudation of blood and fluid. These changes were markedly different from the changes noted in the lungs of patients dying of lobar bacterial pneumonia. A 2011 pathology review of autopsy material obtained from March to October 1918 demonstrated that all 68 cases had some evidence of bacterial bronchopneumonia, often superimposed on viral damage.

Studies in the early 1930's demonstrated that influenza was caused by a filterable agent and that it could be transmitted from a ferret to a human and back again. Later the discovery that the virus could be grown in chicken eggs paved the way for further research and for the development of vaccines. The electron microscope allowed the flu virus to be visualized for the first time in 1943.

Subsequently, a classification system for the influenza viruses was established. There are four types of these viruses: A, B, C, and D. Influenza A, which is the type causing pandemics, has been divided into subtypes on the basis of two proteins on the surface of the virus: hemagglutinin (HA) and

neuraminidase (NA). The hemagglutinin facilitates the entry of the virus into cells, whereas the neuraminidase enables the virus to be released from the infected cell. There are 18 known HA subtypes and 11 known NA subtypes. Hence, numerous combinations are possible. The 2017-8 flu season was dominated by the H3N2 virus. Pandemics in the last 60 years include the "Asian" flu (H2N2), the "Hong Kong" flu (H3N2), the "swine" flu (H1N1).

By 1950, the 1918 influenza virus had not yet been characterized. In that year Johan Hultin, a medical student at the University of Uppsala, was at the University of Iowa studying the body's immune response to influenza under a special program that allowed Swedish medical students to travel to other medical schools for part of their training. On a particular day in January 1950, a visiting virologist offhandedly remarked that the 1918 influenza virus might possibly still be present in affected Eskimos buried in the permafrost. This idea intrigued Hultin and he contacted his faculty advisor, Dr. Albert McKey, about using the search for a permafrost grave as a subject for a dissertation. After obtaining approval of this project, Hultin went about gathering information about the extent of the permafrost and also missionary records about Eskimo deaths and burials in 1918. Finally it appeared that there were only three places with adequate records to indicate burial in the permafrost. Hultin applied to the NIH for a research grant, but heard nothing. Subsequently, it was found that the Army, intrigued by Hultin's idea, was planning it's own expedition to Alaska. Hultin and his colleagues we're able to get a grant from the University of Iowa in 1951 and quickly flew to Fairbanks with jugs filled with dry ice. There was constant rain for several days and the dry ice began to evaporate. They solved that problem by buying several carbon dioxide fire extinguishers, which basically produced "dry ice in powdered form".

Hultin was to be the scout, hiring a bush pilot to take him to the three sites identified as the most likely to have frozen influenza victims. If he found permafrost at a gravesite, he would telegraph the others, which also included an Alaskan based paleontologist. After two weeks, the weather finally cleared and Hultin flew to one of the sites near Nome, but found that the river running through the city had changed course over the years and now was adjacent to the gravesite. Permafrost was no longer present. (Parenthetically the Army expedition with their diesel powered freezers arrived 10 days later and found the same thing.) After a harrowing trip Hultin flew to the next site, the small town of Wales, just across the Bering Strait from Siberia. The cemetery, previously inland, was now on a bluff

overlooking the beach. Again there was no longer permafrost at the gravesite. With great difficulty the pilot was able to fly to the third site, the village of Brevig. There was no place to land, so they landed at a larger town, Teller, 6 miles away. Hultin was then taken in a whaleboat by Eskimos to Brevig where he met the missionary. The gravesite still appeared to be encased in permafrost. Hultin appeared before the village council to explain why he wanted to dig up the graves to obtain specimens and to ask for their permission to do so. Three of the eight villagers living there in 1918 who survived the epidemic were still alive at that time. (72 of the 80 villagers living there in 1918 had died of the flu.) Permission was granted for Hultin to dig.

The other members of the team were notified and arrived to help dig through the permafrost. At a depth of 2 meters several bodies were found. The rib cages of four bodies were opened and specimens were taken from both lungs of those bodies. The still frozen specimens were placed in sterile containers that were then transferred to thermal jugs, where they were kept frozen using a carbon dioxide snow from fire extinguishers.

Arriving back at the University of Iowa, the specimens were cultured in eggs and material was also instilled into the noses of susceptible ferrets. None of the ferrets became ill and no influenza virus was recovered from any of the cultures. Pathologic examination of the specimens revealed acute viral pneumonitis with some sections also showing acute bacterial pneumonia. H. influenzae and S. pneumoniae were cultured from some of the specimens. Unfortunately, none of the materials from this project were saved.

But that's not the end of the story. In the 1990s, the Molecular Pathology Division of the Armed Forces Institute of Pathology developed techniques for obtaining molecular assays from formalin fixed paraffin embedded autopsy tissues. In 1995, Dr. Joseph Taubenberger, a scientist in charge of the Molecular Pathology Division, began a project to recover RNA fragments of the 1918 influenza virus from autopsy tissues in the collection of the National Tissue Repository of the AFIP. A search revealed over 100 autopsy specimens of 1918 influenza victims. 13 of these specimens were thought worthy of further investigation. One of these was shown to be positive for RNA fragments and subsequent sequencing of these fragments revealed that the virus was of the H1N1 subtype. Confirmation from a second specimen was thought to be mandatory. Hultin, then a pathologist in the San Francisco bay area, read about Taubenberger's work in the journal

Science in 1997. He wrote to Taubenberger, telling him about his initial expedition to Brevig and volunteering to return there to obtain additional specimens. After speaking to no one except Taubenberger, Hultin did again fly to Brevig and after a special meeting of the Village Council received permission to reopen the graves and take specimens. A well preserved still frozen obese female body was found, beside which were skeletons and decomposing corpses. It was thought the layer of subcutaneous fat in the obese body protected the internal organs from decomposition during short periods of thawing of the permafrost. Hultin took specimens from the lung, placed them in fixative, and took them back with him to San Francisco. In order to prevent loss in transit, Hultin separated the specimens into four different packages before sending them to Taubenberger. Two were sent by FedEx, one by UPS, and one by the US Postal Service. Studies by Taubenberger's Laboratory revealed that RNA fragments from the Alaska tissue were nearly identical to those from the autopsy specimen. A second autopsy specimen revealed similar findings. The complete coding sequence of the 1918 virus was completed in 2007, using primarily the Alaskan material.

Determination of the complete coding sequence allowed reconstruction of the "extinct" 1918 virus, although some questioned the wisdom of doing so. Senior U.S. government scientists and officials of the Department of Health and Human Services, however, decided that the benefits studying the virus outweighed the risks. The virus is contained in a secure facility in Atlanta, Georgia. Safe protocols for biocontainment and biosafety have been developed. Studies done thus far have revealed insights into influenza virus evolution and transmission factors, as well as a better understanding of the pathology of influenza, the importance of co-infections, and the role of inflammatory responses on disease progression. Studies in mice and nonhuman primates indicate that the 1918 influenza virus suppressed the initial antiviral response as well as activating potent inflammatory responses. These findings may explain the unusual peak mortality in the 20 to 40 year-old victims, in which inflammatory pathologic reactions were prominent.

The 1918 influenza virus is an influenza A virus of the H1N1 subtype. It is thought to have originated in birds, probably wild aquatic birds, but the exact origin is unknown. The viruses causing the pandemics subsequent to 1918, the 1957 "Asian" flu, the 1968 "Hong Kong" flu, and the 2009 "Swine" flu, all contain key genes from the 1918 virus and are considered to be descendants of the 1918 virus. The 2009 virus ("Swine flu") has the same

H1N1 subtype as the 1918 virus. Pigs were thought to have been infected in 1918 during the same time frame as the human infection.

The initial 1918 reconstituted virus was from the September to October peak of the pandemic. Subsequently, virus was reconstituted from earlier months in 1918. A study comparing the two viruses suggested that the earlier virus was more "avian-like", as compared to the later virus, which was more "human-like". Pathologic findings, however, from the two time periods were similar. The study did not explain the unusually high mortality rate in the peak period. A subtle mutation is thought likely but has not been proven. Patients infected with the phase one virus were protected from infection with the phase two virus, also suggesting that the viruses were similar.

History has told us that another deadly pandemic is inevitable. The only question is when such a disaster will occur. Even with all the tools modern medicine has, some have suggested that we are actually more vulnerable than we were in 1918. The world's population is now about four times what it was in 1918 and the number of people living in the slums of lower income countries is greater now than it was then. The current airline infrastructure potentially facilitates the rapid spread of the virus to all the major cities of the world in a matter of days. Many of the drugs that we rely on are made in China. In a pandemic, the supply chain for drugs and medical equipment would be disrupted. The Institute for Disease Modeling estimates that a modern-day global influenza pandemic would kill over 32 million in a six-month period. This would be associated with a severe economic disaster as well. The World Bank estimates that global output would fall by $4 trillion. In order to prevent such a catastrophe from influenza or other pathogens, a coordinated global approach which includes better tools, an early detection system, and a coordinated response system is needed. To mitigate the effects of influenza, a "universal" vaccine, broadly effective against many forms of the influenza virus, is essential. Currently, experts from around the world identify the influenza viruses that are the most likely to cause illness during the upcoming flu season, but their predictions are not always correct. Thus, the seasonal flu vaccine is often less than 50% effective. Several candidate "universal" vaccines are in development. The National Institute of Allergy and Infectious Diseases has recently launched a phase 2 clinical trial of M – 001 vaccine, developed and produced by an Israeli company, BiondVac Pharmaceuticals. This vaccine contains antigenic peptide sequences common to a variety of influenza viruses. Studies in Europe with this vaccine demonstrated that it was safe and well tolerated and that it triggered

an immune response to a broad range of influenza viruses. A second phase 2 trial will be started soon in the United States, sponsored by Baylor University, the University of Iowa, Cincinnati Children's Hospital, and St. Louis University. A large phase 3 trial is planned in Eastern Europe. Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, is setting up a project, the Collaborative Influenza Vaccine Innovation Centers, funded by grants to scientists with different areas of expertise with the hope that a truly universal vaccine will result. Despite these efforts, it is likely that such a vaccine is still several years away. Much more funding is needed for further research.

We also need more accurate and more widely available diagnostic tests, including low cost tests that could be used at home to help making decisions about staying home from school or work. The development of low cost truly effective face-masks, the better promotion of personal preventive habits, and, as previously noted, the cancellation of large gatherings would all be helpful in reducing transmission of the disease. Also essential are annual drills, particularly by hospitals and doctor's offices, to review and update lists of actions to take to deal with a flu epidemic.

Better antiviral drugs are also needed. Tamiflu, (Oseltamivir), which has been available for nearly 20 years, is effective if administered within 48 hours of the onset of symptoms. It reduces the severity of symptoms and also the length of illness by 1.5 to 2.5 days. Unfortunately, Tamiflu resistant influenza viruses have been reported, but they have few and most flu viruses continue to be sensitive to the drug. The H3N2 virus, which was predominant in the 2017-8 high severity season, remained sensitive to Tamiflu. More widespread use of that drug could likely have saved many of the 80,000 American lives lost in the winter of 2017-8. A new antiviral, "Xofluza" (baloxavir marboxil), developed in Japan, has recently been approved in the U.S. Unlike Tamiflu, which prevents infected cells from releasing viral particles, this drug inhibits an enzyme that the influenza virus needs to multiply. In clinical studies, the drug is at least as effective in relieving symptoms as Tamiflu and may be better in limiting transmission. It requires only a single dose, whereas Tamiflu is given twice daily for 5 days. Further studies may be needed since a recent report indicated that a significant number of patients had the emergence of resistant variants after treatment with that drug.

Even in 1918, the vast majority of influenza patients recovered spontaneously. The reason for the rapid development of lower respiratory involvement after a few days of what appeared to be typical flu in those who became seriously ill is unknown. In all influenza pandemics, the groups at highest risks are the very young, the very old, and those with chronic health conditions, so early aggressive treatment of those groups with antiviral agents would seem reasonable. In 1918, however, the 20 to 40 year olds also had a high mortality rate, a situation not seen in other flu pandemics. In any case, if the next pandemic produces the high number of seriously ill patients as seen in 1918, it is unlikely that modern medicine, even in developed countries would have enough ventilators, antivirals, antibiotics, and other supplies to adequately treat all those who became seriously ill.

Another possible treatment approach is the stockpiling of high potency antibodies obtained from those few patients previously infected with influenza who produce those exceptional antibodies. Also in development is an RNA mimic which when introduced intranasally produces an immune response. A special type of ultraviolet light safe for humans has been proposed to kill the virus in the air where people congregate. Monoclonal antibodies, gene therapy, frog mucus, and treatment with natural killer cells are also on the horizon. Researchers at Stanford recently have found that the number of natural killer cells at baseline predicts which individuals will be more likely to become ill with the flu. They have also found a biomarker (a gene called KLRD1) associated with that particular type of immune cell.

In the meantime, before newer antivirals become available, large supplies of Tamiflu or Xofluza must be available on short notice to hospitals and clinics, and possibly as well to schools and other community organizations.

We do not yet have a clear plan for a comprehensive pandemic preparedness and response system. The U.S. Congress has directed the administration to come up with such a plan to strengthen global health security, but thus far that has not been done. Recent tendencies toward xenophobia, isolation and antiscientific thinking are obstacles that must be overcome.

The United States, with our scientific and technical expertise and our influence internationally is best able to lead a coordinated effort in developing such plans. A previous administration spearheaded the global action against the AIDS crisis. Hopefully, our political leaders will step up

and provide similar leadership in confronting the potential threat of influenza or other infectious disease epidemics.

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