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Influenza: historical aspects of epidemics and pandemics

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> If influenza is a riddle wrapped in mystery inside an enigma, then the viral genes are the riddle, the variable surface antigens for which they code are the mystery, and the course and cause of epidemics the ultimate enigma.
>
> E.D. Kilbourne

Influenza is a zoonosis of swine, birds, horses, and humans. Influenza probably existed among mammals and birds in antiquity. As animals became domesticated and human populations became concentrated in urban centers, the transfer of influenza from the zoonotic to the human realm is easy to imagine. Because immunity is short lived because of antigenic drift and antigenic shift, influenza can maintain itself in less concentrated populations. Infectious diseases that confer permanent immunity (eg, measles, smallpox) require large populations to maintain themselves, because after repeated attacks, most susceptible individuals are children who have not been exposed previously. For this reason, influenza affects all ages because of the ephemeral nature of influenza immunity [1–4].

In contrast to plague or smallpox, influenza has the potential for rapid spread. Pandemics can spread from continent to continent and across the world in a few months. Excluding pandemics, influenza epidemics are usually mild, with high attack rates but relatively low rates of mortality (approximately 1%). Although most people in an unimmunized population may be affected by influenza, viral influenza is most severe in women during their second or third trimester of pregnancy, the very young, the elderly, and immunosuppressed individuals. The total percentage of deaths attributable to influenza varies and ranges from 1% to 20%. With large segments of the population affected, even a mortality rate of 1% results in a staggering number of deaths. More people have died from influenza in short periods of time than from any other infectious disease [5–7].

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Influenza viruses

Influenza viruses of the family *Orthomyxoviridae* are of three distinct types: influenza A, influenza B, and influenza C viruses. These single-stranded RNA respiratory viruses are morphologically similar but differ in core proteins. Surface glycoproteins have hemagglutinin (HA) or neuraminidase (NA) activity. There are 15 distinct HAs (numbered 1–15) and nine distinct NAs (numbered 1–9) that define the specific subtype of influenza A viruses. Only three HA subtypes (H1, H2, H3) and two NA subtypes (N1, N2) have caused influenza epidemics.

The influenza viruses are unique among respiratory viruses in their genetic variation. Antigenic drift, minor changes in the surface antigenic configuration, may occur with influenza A, influenza B, or influenza C virus. Major shifts in the antigenic surface determinants occur only with influenza A virus. Influenza A virus is associated with pandemics and the highest mortality and morbidity rates. Influenza B virus has a similar clinical presentation as influenza A virus, but is usually less severe and is common in children and young adults. Influenza C virus does not cause influenza or epidemics, but causes a mild upper respiratory tract infection in children and adults. Influenza B virus pandemics do not occur, and serious disease with influenza B virus usually is confined to the elderly. Croup may be the primary manifestation of influenza infection in young children [3,7,8–10].

Antigenic drift occurs frequently (ie, every few years) with HA or NA. Antigenic drift of HA is mediated by changes in amino acids in five major antigenic sites on the HA molecule. Antigenic drift increases over time after the introduction of a new antigenic variant. The point mutation's response for antigenic drift is linear with influenza viral infections in humans, particularly influenza A virus. Multiple lineages occur in influenza B virus and are more pronounced with influenza C strains. Major antigenic shifts are often a prelude to pandemic influenza. New antigenic variants introduced into a nonimmune population result in pandemic influenza. Waves of influenza infection in an epidemic may be caused by the increasing level of immunity in the population or further antigenic variation in the initial antigenic shift. Influenza A viruses maintain a large reservoir of genetic diversity in their zoonotic hosts in contrast to influenza B and C viruses, which do not have a zoonotic reservoir. Infection to one serotype does not provide cross-protection across subtypes or between influenza A and influenza B viruses.

The significance of multiple lineage evolution in influenza B and C viruses suggests a stable pattern of co-circulating strains in human populations. Changes in the influenza A viruses, which evolved along a single branch lineage, may evolve by clonal reconstitution even after the virus has disappeared. The interaction of avian viruses and human influenza A virus is responsible for antigenic shifts and the reappearance of strains that were seen previously [6,9,11].

Hemagglutination is important in attaching and infecting respiratory epithelial cells, and NA spikes clustered in aggregates on the cell surface are important in the release of influenza viruses from the apices of infected cells. The mechanism of antigenic drift of NA is believed to be the same as for HA in human influenza viruses. The major antigenic shifts have several features in common, including their origin in China, antigenic distinction from circulating influenza viruses, sudden appearance, and limitation to the H1, H2, and H3 variants of influenza A virus. New pandemic strains of influenza A virus may result from avian influenza strains that kinetically interact with human strains of influenza virus. Avian strains also may be transmitted directly to humans, resulting in influenza, as occurred with the pandemic of Hong Kong flu in 1968 (H5N1 and H9H2 influenza viruses). It would seem that this mechanism might have been responsible for the pandemic of influenza in 1918 to 1919 (H1N1). Alternately, it has been proposed that pandemic viruses may remain unchanged and are limited to populations for decades before reemerging in epidemic proportions. This theory also has been postulated to explain the reappearance of influenza (H1N1) in 1977 in China. This strain was responsible for the 1950 epidemic. The H1N1 variant may have been reintroduced after being preserved in an animal reservoir, or from a frozen source, accounting for the long period of inactivity. The influenza A virus outbreak of 1997 (H5N1) was transmitted directly from birds to humans. In 1997, the avian influenza virus (H5N1) affected poultry and humans. As major antigenic shifts are a harbinger of pandemics, antigenic drift occurring in influenza virus during a late spring mini-epidemic (eg, the herald wave) often precedes influenza A or influenza B virus epidemics during the next winter. The antigenic composition of influenza vaccine for the preceding year is based on this principle. Antibodies to HA and NA glycoproteins are protective of influenza infection in humans and are the basis for the components of influenza vaccines [7,9,12,13].

In 1933, Smith is credited with isolating influenza A virus. Burnett was the first person to grow influenza virus in embryonated eggs in 1936. Hemagglutination reactions were discovered by Hirst in 1941. In 1939, Francis isolated influenza B virus. In 1950, Taylor isolated influenza C virus [1,9].

Early descriptions of influenza

It is believed that influenza first appeared in the first half of the 16th century. Caius, the English physician described a ''sweating disease'' in 1551, characterized by headache, fever, and myalgias, that killed some patients in hours but lasted only a few days in survivors. Caius' descriptions are not entirely convincing that he was dealing with viral influenza. The English ''sweating sickness'' did not resemble the influenza epidemic that

occurred in 1173 in England, Germany, and Italy. Subsequent influenza epidemics occurred in Italy and France in 1323. Virtually the entire population of Florence was affected by an influenza epidemic in 1387. The Italians used the expression *ex influentia colesti*, believing that they were under some celestial influence that was responsible for the epidemic. Villaini and Segui modified the term, and it became known as *una influenza* [1,2]. The French referred to influenza as "the grippe," suggesting the acute onset of influenza in which the patient suddenly was seized or gripped by the disease. Further influenza epidemics followed in Paris in 1411, 1414, and 1427. Influenza again returned to Italy in 1414. Although hundreds of thousands of individuals were affected by these early epidemics, there was little or no influenza activity until the 1510 pandemic, which began in Sicily, spread to Italy, and then to the rest of Europe. The 1510 pandemic spread rapidly: The initial outbreak was in July in Sicily and reached northern Italy by August. In September, the pandemic had reached France, and by October, influenza ravaged Holland and Spain [11,13,14].

The first accurate description of influenza is by Sydenham in 1679. Excerpts from his description of influenza are presented [14]:

> For the beginning of this month a cough arose, which was more epidemic than any I had hitherto observed; for it seized nearly whole families at once. Some required little medicine, but in others the cough occasioned such violent motion of the lungs, that sometimes a vomiting and vertigo ensued. On the first days of the disorder, the cough was almost dry and the expectoration not considerable, but afterwards the matter in some measure increased. In short, from the smallness of the expectoration, the violence of the cough and the duration of the coughing fits; it seemed greatly to resemble the convulsive whooping cough of children, only it was not so severe. But it was attended with a fever and its usual concomitants, in which particular it exceeded the convulsion cough, for I never knew that accompanied with those symptoms.

Clinical features of influenza

The incubation period of influenza A virus is from 1 to 5 days, depending on the infecting dose of the virus. Uncomplicated influenza is characterized by a tracheobronchitis and small airway involvement. The onset of clinical influenza is abrupt, and the patient usually is able to cite the hour that the infection began. Influenza begins with severe headache, chills, an unproductive cough, and prominent myalgias accompanied by high fever. Malaise and anorexia are universal. Substernal tightness and chest-wall soreness often accompany the nonproductive cough. Fever peaks on the first day and decreases over the next 72 hours. Patients with high-grade fevers may be delirious, and mild-to-moderate cases of influenza usually resolve within 7 days. Conjunctival suffusion, rhinorrhea, and oropharyngeal erythema are often present. A decrease in fever heralds

increased respiratory symptoms as the virus invades the respiratory tract. Nonproductive hacking cough may contain scant amounts of mucoid and blood-tinged sputum. Weakness, cough, and malaise may persist for weeks after the clinical resolution of influenza. Physical examination is unremarkable except as noted, and the pulmonary findings are scanty. Chest radiograph reveals minimal, if any, infiltrates, which if present are bilateral, symmetrical, and interstitial. Infiltrates and pleural effusions are not part of the clinical presentation. Mild leukopenia is the most common hematologic abnormality, and the erythrocyte sedimentation rate (ESR) is elevated somewhat. Elevations of creatinine phosphokinase (CPK) or aldolase indicate muscle involvement. Rhabdomyolysis may occur in severe cases. Hypoxemia and A-a_2 gradient are related to disease severity [5,7,11,13,15].

A similar syndrome is present in children, except laryngotracheobronchitis (ie, croup) is common in children who usually are younger than 1 year and does not occur in adults. Myalgias secondary to direct muscle invasion of the virus (ie, myositis) is common, affecting the intercostal chest-wall muscle. Gastrocnemius and soleus myositis is more common in children. Nausea, vomiting, and abdominal pain are common complaints in children younger than 3 years, but are uncommon in adult infection. Febrile convulsions may occur in children, but not in adults. Encephalitis may accompany influenza infection [15,16].

Central nervous system (CNS) involvement in adults may be manifested as encephalitis during the influenza attack or after the influenza infection. CNS and cerebrospinal fluid involvement is nonspecific and resembles that of other causes of viral encephalitis. Postinfluenza encephalitis occurs 2 to 3 weeks after influenza infection and is rare. Recovery is the rule for both CNS syndromes. Direct myocardial involvement is not a feature of influenza infection. Toxic shock syndrome may occur in patients infected with influenza who are colonized by toxin-producing strains (toxic shock syndrome toxin 1) of *Staphylococcus aureus*. Influenza may be severe in the second and third trimesters of pregnancy and is more pronounced in smokers and individuals with preexisting lung disease. Influenza is most severe in compromised hosts and is accompanied by a prolonged viral shedding from respiratory secretions [7,9,13,16].

Pulmonary involvement in influenza

The 1957 influenza pandemic was the first to be studied using modern scientific techniques. Most of the current understanding of influenza and its complications are derived from the 1957 pandemic experience. During the 1957 pandemic, it was appreciated that the pulmonary complications of influenza had three different clinical presentations. Firstly, primary viral influenza pneumonia could occur alone without bacterial superinfection. This presentation was uncommon but was the most lethal. Death from

primary influenza pneumonia resulted from profound hypoxemia and was caused by the inability to oxygenate blood secondary to the infection and inflammatory response in the lungs interstitium, the primary site of the influenza infection. Influenza affects the upper and lower respiratory tract epithelium and initially causes a decrease in ciliary function, rapidly followed by destruction of the epithelium. Within days, the respiratory epithelial lining is denuded, and the basal membrane is left exposed. Viral influenza predisposes to bacterial pneumonia by decreasing neutrophil function [8,17]. Bloody, frothy fluid exudes into the alveoli [18]. Patients die a hypoxemic death and literally drown in their own bloody secretions. Except for a red injected face and an erythematous oropharynx, there are few physical findings in these patients. Severe dyspnea and peripheral cyanosis is a bad prognostic sign. Auscultation of the lungs is quiet in most cases, but rarely a few scattered bibasilar rales may be heard. Chest radiograph in patients with primary influenza pneumonia is clear, because the process is primarily interstitial. Minimal scattered infiltrates without pleural effusion are rare. The second form of pulmonary involvement with influenza is simultaneous viral influenza and bacterial pneumonia. These patients are less ill than patients with severe influenza pneumonia. Pleuritic chest pain is not uncommon. Physical findings are those of bacterial pneumonia (ie, localized rales often with a pleural effusion). Chest radiograph shows clear lung fields with superimposed bacterial infection as manifested by focal, segmental, or lobar infiltrates with or without pleural effusion. Combined viral and bacterial pneumonia also has a high mortality rate. Pathogens isolated from such patients in the 1957 influenza pandemic were predominantly *S aureus* [19]. *Streptococcus pneumoniae*, *Hemophilus influenzae*, and group A streptococci also were isolated, as has been reported in the 1918 to 1919 pandemic. Thirdly, patients may present with sequential influenza followed by bacterial pneumonia. After influenza pneumonia, the patient recovers. After a 1- to 3-week interval of improvement, there is a recrudescence of fever and pulmonary symptoms, heralding bacterial pneumonia. Sequential bacterial pneumonia that follows viral influenza is caused by the same pathogens as are found in patients with viral influenza and simultaneous bacterial pneumonia [15,16]. Physical and radiologic findings are the same in simultaneous viral and bacterial pneumonia, but the mortality rate is lowest in this category. The clinical lessons learned from the 1957 influenza pandemic help to explain the discordant findings in studies done related to the 1918 to 1919 influenza pandemic. The three clinical pulmonary variants of influenza were not appreciated when the Spanish flu hit during the years of World War I and thereafter. Apparently, *S aureus* was not an important pathogen in the 1918 to 1919 pandemic. Clinicians now recognize the three clinical presentations of influenza, and empiric antimicrobial coverage is directed against *S aureus*, *S pneumoniae, H influenzae*, *Klebsiella pneumoniae*, and group A streptococci (Table 1) [5,15,16,20,21].

Table 1
Clinical features of influenza pneumonia

Type of influenza	Influenza	Influenza with bacterial CAP (simultaneous)	Influenza followed by bacterial CAP (Sequential)
Usual pathogen	Influenza A virus	Influenza A, B viruses *S aureus* *S pneumoniae* *H influenzae* Group A streptococci	Influenza A, B viruses *S aureus* *S pneumoniae* *H influenzae* Group A streptococci
Days after viral pneumonia	None	3 days after clinical improvement	1–3 weeks after clinical improvement
Symptoms	Dry cough ± mild hemoptysis Pleuritic chest pain Shortness of breath Malaise, restlessness	Same as influenza B virus plus productive cough with purulent sputum ± pleuritic chest pain	Same as influenza B virus plus productive cough with purulent sputum ± pleuritic chest pain
Signs	Fever Dyspnea Cyanosis Hypotensive No rales	Reappearance of fever Localized rales ± consolidation ± costophrenic dullness	Reappearance of fever Localized rales ± consolidation ± costophrenic dullness
Laboratory tests	Profound hypoxemia ↑ A-a_2 gradient ↓ WBC count Sputum: WBCs/normal or no flora	Moderate hypoxemia Mild/no A-a_2 gradient ↑ WBC count Sputum: WBCs/gram (+) cocci or gram (−) bacilli	Minimal/no hypoxemia No A-a_2 gradient ↑ WBC count Sputum: WBCs/gram (+) cocci or gram (−) bacilli
Chest radiograph	No infiltrates No pleural effusion	Focal/sequential infiltrates ± pleural effusions Rapid cavitation with S *aureus*	Focal/sequential infiltrates ± pleural effusions Rapid cavitation with S *aureus*
Mortality	++++	+++	++

Abbreviation: WBC, white blood cell.

Influenza pandemics in history

Influenza pandemics of 1580, 1729 to 1730, 1732 to 1753, and 1781 to 1782

Influenza outbreaks were recognized by their common clinical features, and widespread epidemics occurred in Europe in 1510, 1557, and 1580. The first pandemic followed the 1580 epidemic and spread from Europe to Asia and Africa. Localized epidemics of influenza occurred throughout Europe during the 17th century, but at least three major influenza pandemics occurred in the 18th century. Two major epidemics that occurred at the time were the influenza epidemics of 1761 to 1762 and 1788 to 1789. The pandemics of the 18th century occurred during the years of 1729 to 1730, 1732 to 1733, and 1781 to 1782. The most severe pandemic occurred in 1781 to 1782 and affected North America, South America, and most of Europe [2,9,10].

Influenza pandemics of 1830 to 1831, 1833 to 1834, and 1889 to 1890

During the 19th century, three influenza pandemics occurred in 1830 to 1831, 1833 to 1834, and 1889 to 1890. As in the preceding century, major epidemics occurred between pandemics. There was little or no influenza activity worldwide between the 1847 to 1848 pandemic and the 1889 to 1890 pandemic. The 1889 to 1890 pandemic originated in Russia and devastated Europe before reaching North America in December 1889. Because the cause of pandemics was unknown at the time, flu epidemics were named according to their country of origin (eg, the 1889 to 1890 pandemic was called the Russian flu). After reaching North America, the Russian flu spread to Latin America and reached Asia in February. By March, the flu was pandemic in New Zealand and Australia. In the spring of 1890, the pandemic spread to Africa and Asia. The 1889 to 1890 pandemic was the first pandemic that occurred for which detailed records are available. As mentioned previously, even though the mortality rate in the 1889 to 1890 pandemic was low (ie, approximately 1%), approximately 1 million people worldwide died from this influenza pandemic. Deaths during the 1889 to 1890 pandemic occurred primarily among the elderly. Influenza activity was relatively insignificant for the next 2 decades, and many people regarded influenza as an episodic mild respiratory infection until 1918 [2,5,9,13].

Influenza pandemic of 1918 to 1919

The public health of the world's population was better than it had ever been early in the 20th century. Influenza activity was noted sporadically in the United States in the spring of 1918. Because of American mobilization in World War I, soldiers traversed the country between home and military bases throughout the United States. The numbers of troops rapidly moving about the country was unprecedented, as they traveled from towns to cities to training bases and eventually to ports of disembarkation for Europe.

What was referred to as the Spanish flu seems to have originated in North America. Belligerents on both sides of the Atlantic did not make public details of the flu outbreak because of the effect on troop strength, which had important battlefield implications. Spain was a noncombatant in World War I and was the only country to make public details of their influenza experience in 1918 [2,22].

Epidemiologic evidence suggests that the Spanish flu originated in the United States and was transported by American troops to Europe; after decimating Europe, the influenza pandemic spread worldwide. The 1918 to 1919 pandemic was unprecedented in its virulence and mortality. In the spring and summer of 1919, the pandemic killed hundreds of thousands and infected millions. Unlike previous influenza epidemics, the 1918 to 1919 pandemic affected healthy young adults with an unusually high mortality rate. Another unusual feature was that death in young adults was caused by primary influenzal pneumonia and not complications, as had occurred in previous pandemics. The pandemic occurred in three waves, with each wave bringing increased death rates. After the initial first wave in the spring, the second wave occurred in August, death rates tripled, and the wave subsided in the fall. In the winter and spring of 1919, a third wave occurred before the pandemic subsided. More than a half a million deaths occurred in the United States alone. In terms of fatalities, the 1918 to 1919 pandemic was the single most lethal infectious outbreak to occur worldwide over a 1-year period. It took smallpox half a century to move across Europe and ravage the population. It is still not clear why this pandemic was so virulent. Death rates worldwide in young adults (age range, 20–40) were approximately the same in war-ravaged nations and nations uninvolved in the conflict. Although the virulence of the 1918 to 1919 flu remains unexplained, it has been suggested that its enhanced virulence may have been related to rapid passage from patient to patient, especially in military personnel, which may have elicited an exaggerated immune response, resulting in profound cytotoxic effects in the lungs of healthy young adults [1,2,9,13].

Unusual features of the 1918 to 1919 influenza pandemic

When it was realized that influenza was a pandemic and was killing thousands and thousands of people worldwide, governments tried to keep accurate records of influenza fatalities and called on their public health agencies to control the epidemic and to determine its cause. Unlike previous influenza epidemics, death rates among healthy young adults were higher than rates in the very young and elderly. The most accurate records were kept by the military services, which have complete control over their personnel. In the United States, US Public Health Service records were accurate in large cities, but smaller cities and towns were not included in their surveys. For this reason, details of the fatalities of the 1918 to 1919 influenza pandemic are estimates and are probably greater than reported [2,22].

The exceptional virulence of the 1918 to 1919 strain of influenza baffled medical authorities. Investigators from many countries studied the problem during the pandemic and for decades thereafter without ever determining why young healthy adults were affected preferentially or explaining the lethality of influenza in 1918 to 1919. Investigators reported varied results regarding the causative agent of the pandemic. Conflicting data by first-rate investigators using good techniques failed to come up with a satisfactory explanation for the cause of the pandemic. It had been known from previous epidemics that patients almost always got well after 1 week, even with prolonged postinfluenza mental status changes, malaise, and fatigue. The death rate was approximately 1%, and deaths usually were ascribed to bacterial complications, particularly in children and the elderly. In the 1918 to 1919 pandemic, fit young adults were dying of pneumonia. Some investigators isolated *S pneumoniae* from autopsy specimens of lungs from influenza victims, whereas other researchers isolated *H influenzae,* or group A streptococci. In other reports, no pathogen was isolated, or multiple pathogens were cultured from the lung tissue of fatalities. In 1933, the influenza virus was identified definitively as the etiologic agent of influenza. Bacterial pneumonias superimposed simultaneously or sequentially on influenza pneumonia are the best explanations for the variable findings reported [2,6,22].

The exceptional virulence of viral influenza pneumonia in 1919 to 1918

The exceptional virulence of the flu strain responsible for the 1918 to 1919 pandemic, with its attendant high mortality rate in young, healthy, fit adults, remains a mystery. The flu seems to have begun in August 1918 as sporadic cases in the United States among the civilian population. In August, death rates from flu and pneumonia were slightly above normal but caused no particular concern. The interest of the public was focused on Europe and World War I. Mobilization and training began in the United States to prepare the American Allied Expeditionary Force for European combat.

The first dramatic increases in influenza cases began in the summer of 1918 at Fort Devens, Massachussets, located outside of Boston. Military training centers brought troops together from various parts of the country in high concentration in crowded barracks. Having a few recruits with influenza in overcrowded barracks was the perfect setting for a rapid and extensive influenza epidemic. It became apparent quickly that the conditions were ideal for the rapid spread of influenza and that young, healthy recruits were dying from the infection in great numbers. This phenomenon was a frightful and hitherto unseen. President Woodrow Wilson, by way of the Surgeon General, dispatched Claude E. Welch to investigate the alarming dispatches regarding influenza from Camp Devens. Welch, the most prominent pathologist of the time, arrived at in time to witness the flu outbreak firsthand. He observed and studied the effects of influenza on the

lungs of dead, young recruits. To appreciate and capture the flavor of the time, the following section is excerpted from an account of the initial outbreak at Fort Devens [2,22]:

> Camp Devens, located about 30 miles west of Boston on a well-drained plateau of meadows and woods, had only one characteristic to qualify it for the traditional military epidemic: it was overcrowded, with 45,000 men, 5000 of them under canvas, jammed into an encampment built for 35,000. The cantonment was over capacity for the very good reason that the United States was involved in a war several times more prodigal in its appetite for fighting men than any previous war in history. Where General Grant had called for hundreds of thousands of American soldiers, General Pershing and his French superior, General Foch, called for millions. Thirty-five thousand officers and men had already trained at Devens in the first year of its existence, and almost all of them were already in France. Now the training of the brand new Twelfth Infantry Division was under way. The Twelfth's commander, Major McCain had arrived at Devens on August 20 and announced his firm intention to have the division ready for embarkation to France in 14 weeks. Three weeks later he found himself commander not of a division well on its way to becoming the crack outfit of his dreams, but of a division which was very sick and possibly getting sicker faster than any other similar outfit in the world.
>
> Word of Spanish influenza was heard from Boston as early as the very first days of September, but when the first Devens' victim, a soldier of Company B, 42nd. Infantry, went on sick call on the seventh, his illness was diagnosed as cerebrospinal meningitis. The abruptness of the onset of the disease and the degree to which it overwhelmed the patient—the technical descriptive term is "fulminating"—seemed far too extreme to be attributed to influenza of any kind. After all, influenza, flu, grippe, grip—whatever you called it or however you spelled it—was a homey, familiar kind of illness: two or three days in bed feeling downright miserable, a week or so feeling shaky, and then back to normal. Call it a bad cold or call it flu, it was an annual occurrence in most families and not a thing of terror like smallpox or typhoid or yellow fever. Epidemic maladies like the latter were a danger, not just an inconvenience, and doctors were legally obliged to report them to their boards of health, but few health departments in the United States or the world thought enough of influenza to make it a reportable disease.
>
> The following day a dozen men of Company B showed up at the hospital, apparently with the same sickness as their comrade, and medical officers began to question the original diagnosis. The fever, headache, prostration, and abruptness of onset of meningitis were there, but the most obvious external symptoms were those of disease of the upper respiratory tract: cough, drippy nose, sore throat. The patients complained of aching backs and legs. On September 12 a definite diagnosis of influenza was made. By September 16, 36 members of Company B had been sent to the hospital with influenza and the disease had spread to other companies and regiments. Daily hospital admissions, only 31 on the second day of the month, soared to 142 on the tenth, and to a peak of 1176 on the eighteenth. By that day, 6674 cases of influenza had been reported in Devens. The news

that greeted Welch when he arrived at Devens on September 23 was that 12,604 cases of Spanish influenza had been officially reported since the seventh of the month. How many more mild cases were still in the barracks spreading the epidemic no one could say, but at least the number of new cases of flu being reported was falling off. That number was down 250 from the previous day and had been dropping since the twentieth. But the spread of pneumonia was accelerating. The hospital's clerical system was breaking down under the volume of paper work created by the epidemic, but Colonel Welch could be told that there were at least 727 cases of pneumonia. When the clerks finally caught up with the pneumonia statistics four days later, they discovered that the hospital had 1902 cases of pneumonia under its care and the number was still rising. The Boston Globe reported that in the 24 hours preceding 7 am of September 23, 66 men, all of them probably in the peak years of physical prowess, had died.

The statistics boggled Welch's mind: the sight of lines of sick men shuffling through the cold, penetrating rain to the hospital gave him no encouragement about the immediate future. He needed no stethoscope to conclude that the problem for many of them was lung failure. He could see that at a dozen paces: some of them stumbling along, the blankets over their shoulders soaking up the fine drizzle, were turning blue and even purple.

And when the sick reached the hospital, where was there was room to put them and how many physicians and nurses were there to care for them? The hospital was typical of those thrown together by the army: a maze of dozens of wooden buildings connected by what seemed miles of corridors.

The Devens hospital normally accommodated 2,000; now 8000 sick men needed shelter and treatment. The wards overflowed onto the porches, and when those filled up, raw wooden drafty barracks were commandeered to serve as supplemental hospital—or, rather, as places to bed down the sick until someone, anyone could get around to caring for them. Devens hospital had 300 regular nurses, not nearly enough to handle the tidal wave of patients, and the nurses themselves were, of course, especially susceptible to infection because they were exhausted and constantly in contact with the ill. Welch found that scores of them were down with influenza; at one time 90 of the 300 were incapacitated.

Welch and his colleagues made their inquiries, noted down the appalling statistics (29.6% of the 13th Battalion sick, 17.8% of the 42nd Infantry sick, 24.6% of Trains and Military Police sick), stopped at the hospital laboratory to try to derive some wisdom from the confusion there, and glanced in at the wards with their lines of cots and prostrated soldiers, whose linens were often stained with bloody sputum and the sudden nosebleeds that were symptoms of Spanish influenza. The soldiers with the tint of blue were almost certainly dyeing. The tour was appalling; Colonel Vaughan, who had gone through the Spanish-American War and had seen thousands of cases of typhoid, admitted that he had never, never seen anything so depressing as this. Little could be learned from the sick and dying but that they were sick and dying. Enlightenment, if there was any to be had, would be found in the autopsy room.

Conditions in the morgue were chaotic. In an army camp, populated for the most part with recruits in their twenties, a dozen deaths a week would

be a serious matter. Sixty-three died on the day Welch came to Devens. Presently, 90 would die in a day. Bodies the color of slate were "stacked like cordwood" or lying about the morgue floor in confusion, and the eminent physicians had to step around and over them to get to the autopsy room. There Welch, who had presided over the most famous teaching laboratory for pathology in America for more years than most pathologists had practiced, labored to find the cause of death.

In the open chest of a cadaver, Welch saw the blue, swollen lungs of a victim of Spanish influenza for the first time. Cause of death? That at least was clear: what in a healthy man are the lightest parts of his body, the lungs, were in this cadaver two sacks filled with a thin, bloody, frothy fluid. Many of the dead at Devens had lungs at least similar to the coarse, defiled lungs he had seen so many times before in autopsy, but those were from men who had died 10 days or more after the onset of influenza and after major invasions by the microorganisms commonly associated with pneumonia. The lungs of those who had died quickly, sometimes only 48 hours after the first ache and cough, were such as he had never seen before. There was little or no consolidation of the lung tissue, yet the lungs were so abnormal that pieces of them, which should have been as buoyant as a child's balloon, sank when placed in water. Their most conspicuous feature was the enormous quantity of thin, bloody fluid. It oozed out of the lungs sectioned for examination, and in the large air passages leading to the throat it mixed with air in a bloody froth. As rigor mortis set in, the fluid often poured from the nose and stained the body wrappings.

Welch was little given to fits and starts; he was the most dignified of men, as befitted a hugely successful and universally admired Victorian physician. He was by personality the kind of man who could, to paraphrase a writer of his generation, keep his head while all about him were losing theirs. Furthermore, he was a pathologist and by profession accustomed to a daily routine of horrors. If there was anyone at Devens who could be depended upon as a pillar of strength, it was this sage of Johns Hopkins. But, when he saw the wet lungs of influenzal pneumonia in the fall of 1918, the pillar trembled. "This must be some kind of new infection, or plague" he said.

Two decades later, Doctor Cole remembered that he hadn't been surprised that he and the other younger men had been disturbed, "but it shocked me to find that the situation, momentarily at least, was too much even for Dr. Welch."

What Dr. Welch had observed was primary viral influenza in its most fulminant form. The vivid description of the congested, heavy lungs filled with sanguineous fluid sinking in water is frightening and an indelible memory.

After the 1918 to 1919 influenza pandemic

Encephalitis lethargica

Another unique feature of the 1918 to 1919 influenza epidemic was the encephalitis epidemic that emerged during the next decade. Acute influenza may be accompanied by encephalitis, but symptoms usually resolve without

neurologic sequelae [2,23,24] Postinfluenza encephalitis was described after the influenza epidemics of 1580, 1658, 1673 to 1675, 1711 to 1712, 1729, 1767, 1780 to 1782, 1830 to 1833, 1847 to 1848, and 1889 to 1892. The encephalitis pandemic that followed the 1918 to 1919 pandemic was unique with respect to its frequency, virulence, and sequelae. Von Economo coined the term ''encephalitis lethargica'' in Vienna in 1917. Encephalitis lethargica was characterized by a triad of mental confusion and lethargy, fever, and movements of ocular muscles. Headache, tremors, delirium, and convulsions were common findings. Ocular findings were the most consistent sign of CNS involvement and were present in approximately 75% of cases. Lethargy, for which the malady was named, lasted days to months until eventuating in coma and death caused by respiratory failure. Approximately 80% of the survivors of encephalitis lethargica later developed Parkinson's disease. The causal relations between influenza A virus, encephalitis lethargica, and postencephalitic Parkinson's disease has been supported by a study demonstrating antibody to neutrotropic influenza A virus antigen in the hypothalamic areas of the brain. In idiopathic Parkinsonism, there was no intranuclear fluorescent antibody uptake in the hypothalamic or midbrain areas of the brain, indicating a causal relationship between influenza and postencephalitic Parkinson's disease [25–27].

Summary

Because of the genetic instability of the influenza A virus alone, or combined with an avian or swine strain, the world could experience another influenza pandemic similar to the one in 1918 to 1929. Directly or indirectly, highly virulent strains from an animal or fowl source await the opportunity to infect humans. The spread of influenza is so rapid that a new highly virulent strain could kill millions before enough protective vaccine could be made and distributed. Although vaccines, antibiotics, and ventilators are available, populations easily could be overwhelmed by a virulent influenza pandemic. The public would be as vulnerable as the public was in 1918 to 1919 and would be as terrified and helpless as Welch was in viewing countless influenza casualties [17,23]. The experience of the 1918 to 1919 influenza pandemic should be read as a cautionary tale.

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