Stalking the Wild Influenza

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ABSTRACT Since the 11th Century something like modern influenza has been recognized in both sporadic and epidemic incidence. Called catarrh, flux, “new ague,” la grippe, and even "the la grippe" before influenza became generally accepted, it remained for the pandemics of1889-1890 and 1918 to confer on the ailment the fear and trembling that provoked the governmental response to swine flu in 1976. By 1933, its viral etiology had been recognized and its general pathology well-defined and in 1940, its primary lesion — destruction of respiratory epithelium — confirmed. Periodicity of the process was clearly demonstrated by 1946, setting the stage for efforts at prevention and forcing physicians to be prophetic if uncertain in anticipating which strain of virus will be active when and where.

WHY should anyone get terribly excited about influenza? After two days of misery and a lingering lassitude, the "jolly rant" has run its course, imparting no apparent harm. The puckishness of influenza, suddenly here and gone just as quickly with little acknowledgment of its whereabouts between appearances, only adds to its intrigue. Moreover, influenza's history reflects its peevish personality; our promenades through the early epidemics of vague respiratory maladies, frontier laboratories intent on finding the culpable microbe, society journals and eminent scientists' diaries and even (of all places) the kennels at Mill Hill, England, will illustrate why influenza successfully remained incognito for so many years. The blame is mostly ours, though, for looking for the wrong needle in the wrong haystack.

Influenza's resurgence in the news stemmed from medical experts' warning of a particularly severe epidemic this winter. Our many years' experience and success with antibiotics may inculcate a false sense of security in Americans, but a backward glance at previous epidemics and their sequelae — medical, social and financial — makes it apparent that influenza can still be a fatal and fearsome villain.

Comparisons with the great influenza epidemic of 1918 and that expected this winter were inevitable, since the strain believed responsible for the great epidemic has re-emerged to cause last fall's outbreak among Army recruits at Fort Dix, New Jersey.[1] The “new” virus is perhaps a hybrid of a former flu virus known to infect humans and that influenza virus which causes the disease in pigs. The presence of swine surface antigens makes it virulent to those who lack antibodies to swine virus. Almost 80% of the people exposed during the 1912 epidemic have antibodies, while only 25% of those born after 1925 do.[2] The anxiety that epidemiologists projected was that the majority of Americans are immunologically naked to an influenza epidemic.

The 1918 epidemic did not cause merely a week's inconvenience, but turned victims ashen, drowned them in their own secretions and inspired such names as “the purple death." Two hundred million cases resulted in 20 million deaths 500,000 in the United States alone. While the economic loss was in the millions

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even then. no one can assess the magnitude of personal and social suffering. One public health official estimated that-the Asian flu of 1% and the Hong Kong flu of 1968 each cost the American public in excess of $3 billion.[3] It is incumbent upon us, therefore, for economic as well as scientific reasons, to at least temper the virulence of influenza, the world's only remaining epidemic disease. "Killer diseases" dreaded only a decade or two ago — measles, poliomyelitis, smallpox — have either been brought under control or eradicated. The hope for eliminating influenza lies in careful worldwide surveillance and intel1igent use of vaccines for prophylaxis until eradication is achieved. Moreover, data; from past epidemics helps forecast both the time and antigenic strain of future epidemics.

Just how old is this disease we call influenza and how did it get its name? Historians such as Hirsch, in *Handbook of Geographical and Historical Pathology,* [5] and Creighton, in his *History of Epidemics* in *Britain,*[6] document early epidemics of respiratory disease going back to the 11th Century, and given the rapid and "extensive spread of a disease characterized by a short course, minimal fever, and prostration far in excess of catarrhal symptoms, it is likely that many of these epidemics and pandemics were in fact influenza.

The term "influenza" did not always signify the specific disease that it does today. Leichtenstern viewed the word as an outgrowth of the Italian *influenza di freddo*—the influence of cold.[7] This derivation of the Latin *influxio,* meaning catarrh, may be an outgrowth the humoral pathology, but "influence," however, has more often been used in reference to sidereal compellation of human activities than to natural phenomena. The Parisian Comte de Mezeray[8] writes about the

> violent and extensive catarrhal fever in 1510, of that kind which the Italians call influenza, thus recognizing an inscrutable influence which affects numberless persons at the same time … The physicians shortened life not a little by their purgative treatment and phlebotomy, seeking an excuse for their ignorance in the influence of the constellations, and alleging that astral diseases were beyond the reach of human art.

At the tum of the 17th Century, "influenza" designated only a general "flux" or fever; thus we can read Dr. Molyneaux's account of 1694 in the *Annals of Influenza* [9] that "so general did this influenza rage that few or none escaped." The term was vogue in the New World, too, for in 1699 Samuel Maverick wrote that "the flux, agues, and fevers, 'have much rained in both cittie and country ... especially about Boston, where have dyed very many."[10]

In 1712, Britain introduced the term "new Ague," born of the Old French *agu,* meaning a sharp or violent chill. The French, however, preferred to call influenza *La grippe,* which suggests a sudden fantasy or caprice *(prendre en grippe* means to tum against someone), while the Germans dubbed it *galanteriekrankheit* — all of which imply "the disease in vogue." Recall that this was the Age of Manners and that it wouldn't do for the elite to have a disease out of fashion; influenza, in its many aliases, was apropos of a sometimes mild disease that was not as esthetically repugnant as the then common cholera, pox and gout. The term *la grippe* lasted well into the 20th Century in this country. In fact, American soldiers fighting in France during World War I referred to epidemic influenza as "The La Grippe" — redundant but effective.

Boston's Noah Webster, in his *History of Epidemic and Pestilential Diseases Etc.,*[11] recounts the influenza of 1647: "This year appeared an epidemic catarrh in *America,* and the first of which we have any account." It began in the Massachusetts Bay Colony, swept the remaining country (mainly the Northeast then) and continued to the West Indies, which were French colonies at the time.

By the end of the 18th Century, the term "influenza" had become both popular and vague. Most outbreaks were not severe enough to have such highly characteristic symptoms as did the pandemic of 1918, and many eases of influenza, the common cold and other respiratory infections were probably lumped under the term' 'influenza. " Little wonder that early physicians fared poorly in effecting a cure; since they were ignorant of "real" influenza's existence, one should not be too critical of their invoking celestial culpability.

It was perhaps Parkes[l2] in 1870 who first "sensed" that influenza was not merely a catchall catarrhal malady but a distinct, highly characteristic disorder:

> The symptoms of influenza are compounded of two conditions — a general fever of determinate duration and a marked and evidently specific affection of the mucous membrane of the nose, mouth, throat and respiratory tract, which also has a determinate course .... [Symptoms] last four or five days usually — sometimes they continue ten or twelve days but this is generally when pneumonic complications supervenes.

While Parkes and others labored to define the enemy, Pfeiffer[13] sought its etiology in 1892 and began the bacterial vs.

viral battle, which lasted 41 years. Pfeiffer's original paper reports on 31 cases, six with autopsy, from the great pandemic of 1889–1890. In all cases he found gram negative rods, sometimes in great numbers and uncontaminated by other organisms. This "influenza bacillus" (now known as *Haemophilus influenzae)* acquired Pfeiffer's name, and while we now know it as a frequent complication and not the cause of influenza, it is easy to see why Pfeiffer's bacillus was widely accepted as the etiologic agent until the pandemic of 1918.

Pfeiffer was bead of the research department of the prestigious Berlin Institute for Infectious Diseases, and his integrity and unquestioned reputation were based on previous research on cholera and typhoid fever. He was a colleague of Koch, Flügge and Kolle. If one had any faith in scientific method, Pfeiffer's error had to be believed; it certainly won the accolade of Hans Zinsser, who wrote in the 1919 edition of his *Textbook of Bacteriology* that "the relationship between the clinical disease known as influenza or grippe and the Pfeiffer bacillus has been definitely established by numerous investigations."[14] (Parenthetically, Pfeiffer never fulfilled Koch's third postulate that a pure culture must cause a disease in healthy animals identical to the naturally occurring one.)

Bloomfield and Harrop[15] contributed to the semiology of influenza by studying the clinical symptoms in young people during the great pandemic of 1918. They delineated a disease of highly fixed characteristics, emphasizing the sudden onset with constitutional symptoms of headache, myalgia and prostration; facial flushing; typical palatine eruptions; diffuse respiratory tract inflammation; fever of definite duration; leukopenia and a high incidence of superimposed bacterial lung infection. Many investigators doubted that Pfeiffer's bacillus, normally saprophytic, could suddenly attain worldwide virulence. Many viewed it as a pathogen in search of a disease. As the October 5, 1918, issue of the *Journal of the American Medical Association* summarized, "the 'influence' of influenza is still veiled in mystery."[16]

Lord, Scott and Nye,[17] reporting from the Massachusetts General Hospital in 1919, illustrated that in Boston and elsewhere there were cases of influenza in which Pfeiffer's bacillus could not be isolated and others in which the staphylococcus and pneumococcus predominated, yet associated with the same clinical picture. They presented a clear-cut argument against the influenza bacillus:

> During the interepidemic period, however, those cases which show influenza bacilli as a practically pure infection present no clinical or pathological differences from respiratory infections in which other organisms predominate and in which influenza bacilli cannot be found.… [The bacillus] is a common invader of the normal respiratory tract and may be found in a considerable proportion of cases with pulmonary tuberculosis and the contagious diseases of childhood. There seems to be no justification for the belief that the epidemic was due to the influenza bacillus, which is probably a secondary invader and bears about the same relation to the influenza cases as to respiratory infections of a different sort.

In 1920, only one year later, however, Blake and Cecip8 repeated Pfeiffer's experiments of 1893, in which he inoculated the pharynx of monkeys with cultures of *Bacillus influenzae.* They interpreted their experiment much less critically than did Pfeiffer and concluded that they had produced an experimental disease identical to influenza in man. "It seems reasonable to infer *that B. influenzae* is the specific cause of influenza." Clearly, the end of this controversy was not in sight.

With so much energy devoted to influenza, one could reasonably expect a number of serendipitous achievements, some more notable than others, such as Fleming's discovery of penicillin. Pure cultures of Pfeiffer's bacillus were notoriously difficult to grow, and Fleming sought a way to inhibit their contamination by common cocci, a problem solved by that famous uninvited *penicillium* colony which killed the cocci, leaving Pfeiffer's bacillus sole heir to a bountiful agar. After showing penicillin's usefulness in isolating the bacillus, Fleming suggested that the mold "may be an efficient antiseptic for application to or injection into areas infected with penicillin-sensitive microbes."19 On the less memorable side of ancillary achievements, influenza was immortalized in these meanderings of an anonymous Illinois medico:[20]

> ?Flu?
> If we but knew
> The cause of Flu
> And whence it comes and
> what to do,
> I think that you
> And we folks, too,
> Would hardly get in such a
> stew.
> Do you?

In pathology, MacCallum[21] was the earliest to recognize, albeit vaguely, two separate lesions in patients who died of pneumonia after influenza infections. He vividly described the changes now recognized as interstitial viral pneumonitis:

> The wall of the bronchus is greatly thickened by infiltration of mononuclear cells with a

> few leukocytes, and by the new formation of connective tissue cells. The alveoli contain an exudate . . . which is often predominantly composed of desquamated epithelial cells and dense fibrin. In this exudate it is rarely possible to find influenza bacilli .... The sharp contrast between this form and those produced by the pneumococcus and streptococcus is very evident.

MacCallum did not fully appreciate the significance of the interstitial pneumonitis he so aptly described, yet concluded that he saw no difference in the pathological changes produced by Pfeiffer's bacillus and the pyogenic cocci:

> But now that it appears the streptococci and influenza bacilli may in precisely similar ways be governed, as regards the character of the lesions they produce ... it seems unnecessary to ascribe one type of lesion to the streptococcus and another to the influenza bacillus.

During the next few years, various investigators conducted rudimentary experiments in the transmission of influenza between human volunteers. Most results are equivocal because of the vague identity of both the donor disease and the recipient infection. The drastic experiments of Rosenau[22] deserve mention because their unorthodox methodology contrasts so sharply to the rigid ethical restraints in human experimentation today. Rosenau's volunteers had their throats swabbed with the secretions of, breathed muzzle-to-muzzle with, were coughed upon by and sustained intimate contact with multiple hospitalized influenza victims — but not one of his volunteers contracted influenza!

The idea of viral diseases was emerging in 1914 as Kruse swabbed the filtered secretions of common cold sufferers into the noses of healthy subjects, thereby transmitting the cold to the volunteers. *Two* y.ears later, at a Boston symposium of flu and pneumonia, Rosenau suggested that influenza might be caused by a virus that could pass a bacteriologic filter "in accordance with the work of Krause [sic] of Vienna."[23] Scattered reports of a virus–like organism as the etiologic agent of influenza were announced from various parts, but most left much to be desired in terms of controls, positive identification of the disease produced, lack of confirmation of preliminary findings by subsequent investigators and the difficulties in propagating the "virus" in artificial media.

In 1921, the British Medical Research Council decided that the study of canine distemper would enlighten us about the analogous disease of human influenza. The economic blight that canine distemper caused for fox hunters and dog lovers prompted their contribution of £37,000 to the project, more than twice the amount allocated by the government. The search for the distemper microbe was undertaken at the National Institute for Medical Research Farm Laboratories at Mill Hill, England. The kennels and laboratories were models of aseptic technique and painstaking effort paid off handsomely when Dunkin and Laidlaw isolated the virus in 1926. After field testing by numerous kennel clubs, an effective canine distemper vaccine was commercially available by 1929.[24]

The knowledge gleaned at Mill Hill was put to good use, and the first convincing evidence for a vital etiology of influenza came from Smith and co-workers.[25] Their first attempts at infecting lab animals with throat washings from victims of the 1933 British epidemic were unsuccessful, but since the Old World ferret, that toothsome cousin of the weasel, proved superior to dogs in contracting canine distemper, Smith suspected that ferrets might be conveniently susceptible to influenza. He was right.

Work was immediately transferred to the rigid environment of Mill Hill, where their well-designed experiments led them to conclude:

> The infectivity of the filtrate, coupled with the fact that we failed to grow anything from the filtrate, has convinced us that we are dealing with a true virus disease.

Their discovery of neutralizing antibodies was serendipitous: ferrets that recovered were immune to subsequent infections and the serum from these convalescent weasels neutralized cultures of the virus.

Research in the immunity and transmissability of the now–proven influenza virus was prominent during the next few years. Another milestone was reached in 1935 when Smith[26] described the method of chick egg inoculation. But it was Burnet,[27] five years later, who described the pathological findings in the recovered embryos; namely, the destruction of the respiratory epithelium as the primary lesion. Up to this point, investigators of influenza, unbeknownst to them, had been working only with influenza A, then called strain PR8. In 1940, several virologists[28] reported that convalescent sera from patients suffering from what clearly was influenza contained no neutralizing antibodies. Francis[29] Was able to produce experimental influenza in ferrets with inoculum obtained from victims of a New York outbreak, but this particular influenza virus, subjected to the current immunological armamentarium,

defied identification as the previously isolated influenza A strain. In true scientific form, Francis simply dubbed this virus influenza "B" and was later able to differentiate A from B by complement fixation. Shortly thereafter, numerous papers spewed forth reports or speculation about other immunological types of influenza. Research into the subtle nuances of antigenic relationships among various strains of the virus continues even today.

Perhaps the milestone of "classic" influenza research with the greatest clinical importance is the report of the Commission on Acute Respiratory Disease from Fort Bragg, North Carolina, in 1946.[30] This group's work forms a cornerstone of modern epidemiology as well, for it examined data from 16 epidemics between 1920 and 1944 and derived a model for the periodicity of influenza epidemics in the United States. Their conclusion that influenza A occurs in cycles of two to three years and B in cycles of four to six years remains valid and has been an important tool in forecasting epidemics.

Lastly, the history of vaccination against influenza should be mentioned. During the epidemic of1918, the "vaccines" consisted of concentrated, killed organisms cultured on artificial media. *The Report of a Special Committee of the Public Health Association* acknowledge that vaccines had to be used on the chance that they bore some relation to the unknown organisms of influenza, adding that there were no grounds that the vaccines were at all efficacious. Even in the 1940s, vaccines produced in embryonated eggs did not impart much immunity, mainly because they were not potent enough to elicit adequate antibody titres and because the strains of vaccine were not sufficiently similar to those causing epidemics, and so failed to inveigle the influenza. [32]

During 1946 to 1953, Francis, Salk, Horsfall and others[32] developed procedures to concentrate and inactivate influenza A and B vaccines, select and propagate desired strains and amplify vaccine immunity with adjuvants. Their fruitful work led to the modern science of specific strain vaccine manufacture, our main weapon in influenza prophylaxis.

It is not the purpose of this article to outline the data and trends of modern influenza virology. Rather, it has chronologically presented the base of data upon which that modern science rests, tracing the trail, as it were, that "frontier scientists" followed in their effort to combat what for many centuries was an unknown and mysterious disease, and showing how such slow, painstaking and methodical work may ultimately eradicate this last deadly, epidemic enemy.

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