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THE INFLUENZAS OF SWINE AND MAN[1]

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IN THE late summer or early autumn of 1918 a new epizoötic disease appeared among swine in the Middle West. The exact date or locality of its first occurrence remains unknown but careful observers state that cases were seen as early as August on farms in western Illinois. It is certain that the disease caused serious losses among swine on exhibition at the National Swine Breeders' show held in Cedar Rapids, Iowa, from September 30th to October 5th. At the conclusion of the show, the swine, many of them ill, were returned to their home farms and, within 2 or 3 days, this new disease was stated to be rampant in the portion of the drove that had remained at home. Shortly thereafter it became widespread among swine herds in Iowa and other parts of the Middle West. The epizoötic persisted in various localities until January of 1919 and reappeared in the autumn and winter of that year as extensive and severe as in 1918. It has recurred each year but varies annually in its severity and extent.

According to Dorset, McBryde and Niles (1), Dr. J. S. Koen, an Inspector in the Division of Hog Cholera Control of the Bureau of Animal Industry, was the first to recognize the disease as being different from any previously encountered. He was so much impressed by the coincidental prevalence of human influenza and by the resemblance of the symptoms seen in man to those occurring at the time in hogs that he became convinced that the two were actually the same. He therefore gave the name of "flu" to this new disease of hogs. The opinion of Koen that "flu" represented an entirely new swine epizoötic disease, and that swine might have been infected in the first instance from man, was

shared by some veterinary practitioners and many farmers in the Middle West (2). Furthermore, the name "flu," prefixed by the word "hog" or "swine" proved a generally accepted designation for the condition. Since the disease has entered the period of scientific investigation, it has been dignified by the name "swine influenza."

CLINICAL FEATURES OF SWINE INFLUENZA

Swine influenza is essentially a disease of autumn and early winter occurring annually among hogs in the middle western states. Its onset is sudden and the morbidity rate in an affected herd high; practically all of the animals under one year of age become sick. Fever, anorexia, prostration of an extreme type, cough, and a rapid peculiar abdominal type of respiration are salient features of the disease. The animals cry out when handled, which has been interpreted as evidence of muscular tenderness. A leucopenia is usually to be observed (3). The period of illness is short, varying from 2 to 6 days, and in uncomplicated cases recovery is almost as sudden as the onset. The mortality usually ranges from 1 to 4 per cent, but may be higher.

EXPERIMENTAL TRANSMISSION

Swine can be readily infected experimentally by intranasal inoculation with suspensions of diseased lung or bronchial exudate (3, 4). The disease is also highly communicable, transmitting with ease by pen contact. Experimentally produced swine influenza is clincally similar in all respects to that observed occurring naturally in the field. Its incubation period is short; from 2 to 7 days for animals infected by pen contact, and from 24 to 48 hours for animals infected by intranasal instillation. Death may ensue on from the 3rd to the 6th day of illness, or later. It is preceded by an exaggeration of all respiratory symptoms, an increase in the prostration, the onset of an active, incoördinated delirium, and a progressively intensifying cyanosis. The mortality rate for experimental swine influenza is something under 10 per cent.

PATHOLOGY

Swine naturally or experimentally infected with swine influenza, and killed on from the 3rd to the 5th day of illness, show a similar picture at autopsy. The cervical and bronchial lymph-nodes are swollen and edematous. The trachea contains a white, glassy, tenacious mucous exudate in from moderate to copious amounts. There is more exudate in the large bronchi, and in the smaller bronchi and bronchioles it completely fills the lumen. In the bronchioles it is of firmer consistency than higher in the respiratory tract and can frequently be removed in small, white, semitrans-lucent, sago-like masses. The pleurae are usually free of excess fluid or fibrin. The lungs present very constant and characteris-tic gross changes as depicted in figs. 1 and 2. The involved part is purplish-red in color, depressed, firm, and "leathery," does not crepitate, and is friable in contrast to its usual rubber-like con-sistency. The cut surface is moist and the small bronchi exude a thick, glassy, white mucous exudate. The gross picture is that of an atelectatic pneumonia, variable both in amount and distribu-tion, but limited usually to portions of the apical, cardiac, and azygos lobes and not infrequently involving all five of these. The adjoining lung tissue is emphysematous, exaggerating the depressed appearance of the pneumonic areas.

In fatal cases the postmortem picture is somewhat different. There is often a serosanguineous pleural exudate which sometimes contains fibrin. The lungs are voluminous, heavy, and mottled purplish-red in color. Only the apical, azygos, or cardiac lobes are consolidated. Thus the true pneumonia is limited to the same portions of lung involved in nonfatal cases. The diaphragmatic lobes, which in swine comprise well over half the actual lung sub-stance, exhibit a hemorrhagic type of pulmonary edema which is in most instances extreme. The markings of the interlobular septa are widened by fluid and the lobes, as a whole, have a glis-tening swollen appearance. When they are cut across there is an outpouring of a frothy, bloody fluid.

Outside the respiratory tract pathological alterations are vari-able and probably not of great significance. The spleen is some-
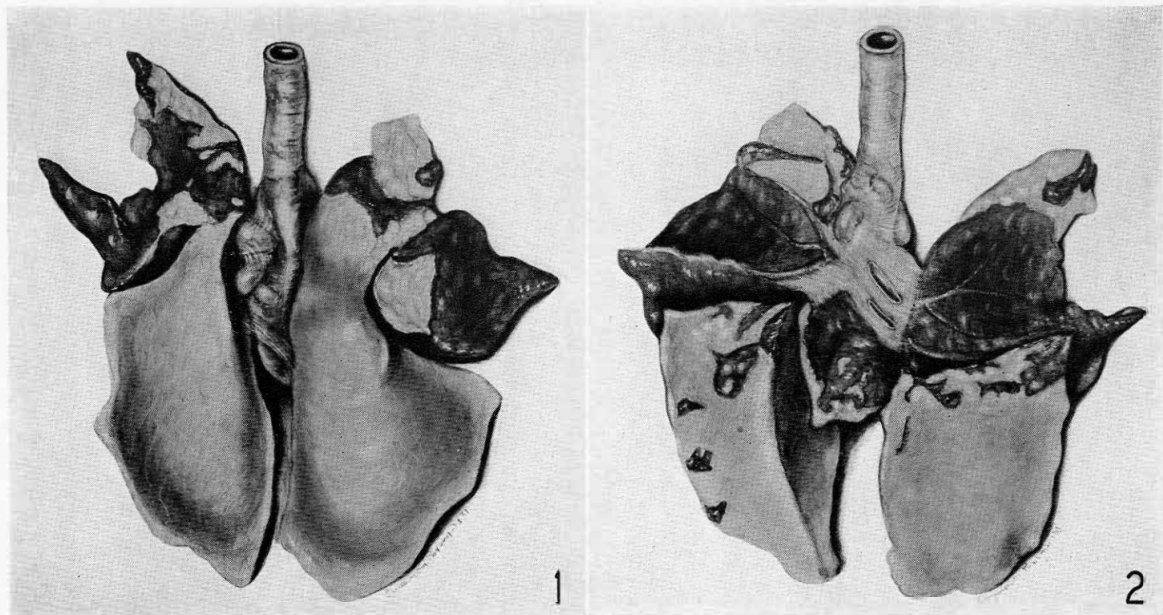
FIG. 1. Dorsal aspect of lung in experimental swine influenza to show the typical appearance and distribution of the atelectatic pneumonia. The lymph-nodes at the hilum are swollen and edematous. The sharp demarcation of the pulmonary lesions is noteworthy. Animal chloroformed on the 4th day of illness.

FIG. 2. Ventral aspect of same lung.

times moderately swollen, the mesenteric lymph-nodes are usually edematous, the gastric mucosa is frequently hyperemic, and the stomach empty except for thin, bile-tinged mucus. The mucosa of the colon often exhibits mildly edematous hyperemic patches overlain by a scant catarrhal exudate.

Histopathology. The histological alterations in the respiratory tracts of swine sacrificed on from the 3rd to 5th day of illness may be briefly described as follows:

Tracheal sections show little that appears abnormal.

Lung sections, cut in such a way as to include small bronchi and bronchioles, exhibit the following features. The small bronchi and bronchioles are filled with a polymorphonuclear leucocytic exudate (figs. 3 and 4). Bacteria are never numerous in this exudate and frequently they are not demonstrable. The cilia lining the smaller bronchi are either entirely gone or badly matted together. The lining epithelium is fragmented, in places partially desquamated, and the cytoplasm of many of the cells appears vacuolated (fig. 5). In the spaces created by the fragmentation of the lining epithelium, leucocytes, singly or in clumps, are sometimes seen. There is an extensive peribronchial round cell infiltration (figs. 3 and 4). The areas of lung involvement are of lobular distribution and sharply demarcated from adjacent uninvolved lung by interlobular septa, although a number of adjacent lobules may be, and usually are, affected. In these areas the alveoli are collapsed and frequently contain desquamated epithelial cells, small numbers of mononuclear cells and occasionally some coagulated plasma (figs. 3 and 6). Large, feebly stained cells exhibiting a "foamy" cytoplasm are especially numerous in some sections. Leucocytes and red cells are not numerous in the alveoli although it is difficult to find sections, even from very early cases, in which the alveoli in some areas do not contain accumulations of them. When present, leucocytes are most abundant in the alveoli opening directly into the terminal bronchioles. The alveolar walls are wrinkled, thickened, and infiltrated with mononuclear cells (fig. 7). Dilated capillaries in the alveolar walls are packed with red blood cells, and widened lymph channels in
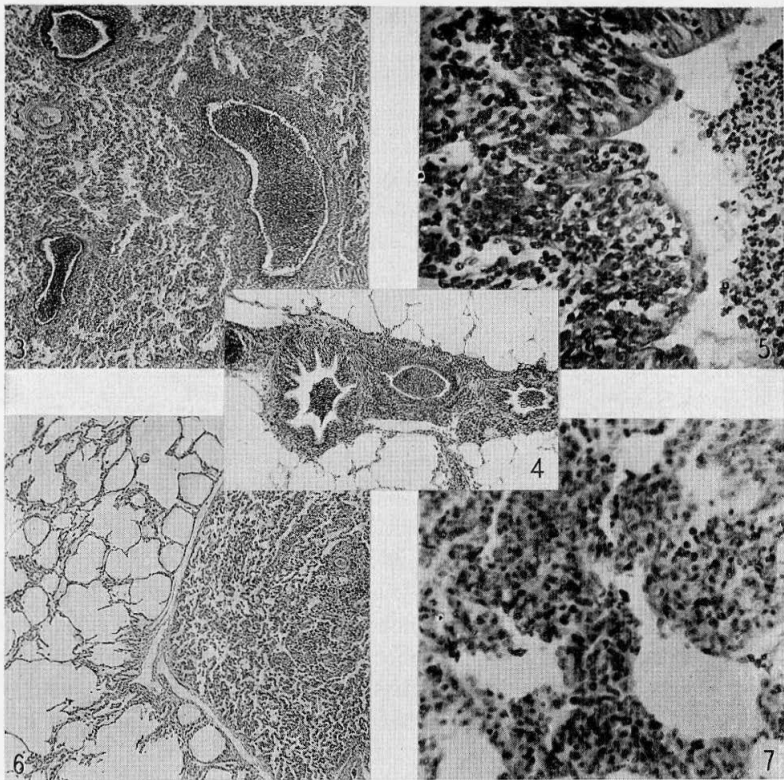
FIG. 3. Section from the lung in experimental swine influenza showing dense leucocytic exudate in small bronchi, peribronchial round cell infiltration and surrounding atelectasis and interstitial pneumonia. Animal chloroformed on 5th day following inoculation. Eosin-methylene blue. × 33.

FIG. 4. Section of lung from a spontaneous field case of swine influenza showing a bronchus in an area of compensatory emphysema to illustrate better the dense peribronchial round cell infiltration. The lumen of the bronchus is packed with leucocytes. Animal stunned and bled to death. Eosin-methylene blue. × 33.

FIG. 5. Section of a small bronchus in experimental swine influenza showing leucocytic bronchial exudate, fragmented and vacuolated epithelium denuded of cilia, and round cell infiltration of the submucosa. Leukocytes have invaded the mucosa. Animal chloroformed on the 5th day following inoculation. Eosin-methylene blue. × 195.

FIG. 6. Section of lung from a spontaneous field case of swine influenza showing atelectasis with round cell infiltration of the alveolar walls, scant leucocytic exudate in some of the collapsed alveoli, and compensatory emphysema. Animal stunned and bled to death. Eosin-methylene blue. × 33.

FIG. 7. Section of lung in experimental swine influenza showing round cell infiltration of alveolar walls in an area of atelectasis. Animal chloroformed on 3rd day following inoculation. Eosin-methylene blue. × 188.

the interlobular septa are filled with coagulated lymph and small numbers of cells.

Histological examination of lung sections from fatal cases reveals a picture similar to that described for nonfatal cases but modified by the presence of an intense edema and congestion.

ETIOLOGY OF SWINE INFLUENZA

In view of the economic importance of swine influenza, it had been surprisingly little investigated at the time Dr. Paul Lewis and I began our studies. Several organisms had been suspected as responsible (4, 5, and 6) but the results obtained in attempting to infect swine with them were not convincing. In addition to the confusion regarding its etiology, the opinions of veterinarians and farmers in the Middle West that the disease represented pandemic human influenza surviving as an infection of swine made the problem one of broad interest, since it seemed possible that anything we learned concerning the etiology of swine influenza might later prove applicable to the human disease.

A Hemoglobinophilic Bacterium in Swine Influenza. Our studies were begun in November of 1928. Infectious material in the form of bronchial exudate and pneumonic lung was obtained from swine in eastern Iowa where an epizoötic of swine influenza was then in progress. Two strains of the disease were established in our experimental swine and maintained by serial passage at 4- or 5-day intervals. The respiratory tracts of all experimental animals were studied bacteriologically at autopsy. An organism similar to Pfeiffer's *H. influenzae* was obtained in pure culture from both first passage swine inoculated with each of the strains. The same bacterium was isolated thereafter from all swine infected in later passages, with either strain of the disease, provided they came to autopsy within 7 days following the onset of fever. Frequently no organism other than this influenza-like bacillus could be recovered from the lungs or the bronchial exudate of infected animals. Here then in swine influenza was an organism like that believed by many to be responsible for influenza in man. The problem of determining the etiology of swine influenza seemed absurdly simple in the beginning for while the bacillus, which we

named *Hemophilus influenzae suis* (7), was not easy to cultivate, it could always be isolated from cases of the experimental disease by appropriate methods. The very difficulties encountered in its isolation and its fastidious requirements of particular media upon which it could be grown seemed to emphasize its importance. In addition, there were numerous cases in which it was the only organism that could be isolated; in these there was no choice but to consider it of etiological importance, unless we wished entirely to deny it a rôle in the disease.

It was, of course, obvious that if the organism were actually the cause of swine influenza it should fulfill Koch's postulates. The first pig inoculated intranasally with what we believed to be a pure culture became ill. The lesions produced were similar to those of swine influenza, and the organism was recovered in pure culture from the respiratory tract. The problem seemed simpler than ever and we were by now convinced that *H. influenzae suis* was the agent responsible. When we repeated the experiment in a second pig, however, we failed to obtain an infection. The animal remained perfectly normal and no lesions suggestive of influenza were to be seen when it was killed after a period of observation. Four other pigs inoculated intranasally with pure cultures of the organism likewise remained normal and we began to doubt the first experiment and the correctness of the view that *H. influenzae suis* caused swine influenza. Even now, there is no certain explanation of that first positive experiment, provided indeed the animal actually had influenza as was believed at the time.

Since the first experiment was performed with a culture that had been transferred only four times on artificial media, we considered for awhile the possibility that we were dealing with a bacterium that very rapidly lost its virulence under cultivation and tried various means to restore its hypothetical pathogenicity. These were unsuccessful and, because our strains of the disease maintained by continuous serial passage in swine were finally lost, work for the year was discontinued.

The following year the swine influenza epizoötic in Iowa was less severe and extensive than that of 1928. Four strains of infectious material were obtained and transmitted to our experimental swine.

Again *H. influenzae suis* was regularly encountered in animals ill of the experimental disease. In addition, the organism was cultivated from six field cases in five different herds. Freshly isolated pure cultures were again found harmless for swine of proven susceptibility. The 1929 strains of the disease could not be maintained for long by serial passage and only about one month's work was possible.

In 1930 two new strains of swine influenza were obtained in Iowa. These proved readily transmissible and again *H. influenzae suis* was the predominant or only organism that could be cultivated, but all efforts to produce the disease with these new cultures were unsuccessful.

A Filtrable Virus in Swine Influenza. A few attempts to infect swine by administering bacteriologically sterile Berkefeld filtrates of known infectious material intranasally had been made during the first year's work. No illness remotely resembling swine influenza had resulted and the experiments were considered negative. By 1930 when *H. influenzae suis* had failed so miserably to fulfill the requirements of an etiological agent, we were again ready to consider the question of a virus etiology in swine influenza.

Swine were inoculated intranasally with Berkefeld V or N filtrates of known infectious lung and bronchial exudate suspensions and autopsied in 4 or 5 days. Of 10 experiments, 3 were interpreted as negative, while in the remaining 7 some evidence was obtained that the injected filtrate had contained an infectious agent. The illness induced by this filtrable agent, however, was definitely not swine influenza and will be referred to hereafter as "filtrate disease" (8).

Clinically the filtrate disease is much milder than swine influenza. Sometimes it is so ill-defined that infections are difficult to recognize. In most cases there is no elevation of temperature, while in a few a fever for one day is observed. This is at marked variance with the 4- to 6-day fevers seen in typical swine influenza. The usual symptoms shown by filtrate-inoculated swine are a moderate and transient apathy, some diminution in appetite for a period not exceeding 3 days, occasionally a slight cough, and, as in swine influenza, a moderate or marked leucopenia. The extreme prostration so common in swine influenza is not seen.

The lesions are slight as compared with the 4- and 5-lobe pneumonias of swine influenza. The lungs show only a scant, scattered, patchy, lobular atelectasis involving as a rule not more than small portions of one or two lobes.

Histologically the bronchial epithelium is found to be damaged; there is a heavy peribronchial cuffing with round cells and the alveolar walls are wrinkled, thickened, and infiltrated by round cells. The collapsed alveoli are usually free of cells and, in contrast to swine influenza, no leucocytes are present, as a rule, in the lumen of bronchi or in the alveoli of involved areas of lung.

The filtrate disease proved transmissible in series and passage did not modify its character, thus indicating that its mild nature had not been due to dilution of the inciting agent during filtration. Furthermore, it proved highly contagious.

The filtration experiments indicated that infectious material from experimental cases of swine influenza contained an agent capable of passage through Berkefeld V or N filters and possessing slight but definite pathogenic properties for swine when administered intranasally. Subsequent investigation has shown that this agent possesses all the properties requisite for its classification as a filtrable virus (8).

H. influenzae suis, while constantly encountered in cultures from animals with typical influenza, was not present in those suffering the filtrate disease; not infrequently their respiratory tracts proved bacteriologically sterile.

Following the establishment of the presence of a filtrable virus in swine influenza, the situation, as to the etiology of the disease itself, became even more confused than it had been when *H. influenzae suis* was suspected. Here, instead of one agent that could be looked upon as of possible etiological importance, were two such agents. The organism could not be completely ignored, for, while it was apparently perfectly harmless for swine, its constant presence in so many samples of infectious material from the field and its persistence on serial passage through experimental swine kept attention focused upon it. Neither could the filtrable virus be accepted whole-heartedly as the cause of the disease because, while it unquestionably possessed pathogenic properties

for swine, the mild illness that it caused was certainly not swine influenza. The dilemma was perplexing. Considered in the light of views current that an infectious disease was caused by a single agent, we had reached the point in our experiments where it appeared that we had one too many under suspicion. For awhile it seemed essential to choose between the two. It may be pointed out that this situation was not unique to our problem: for years, investigators of human influenza had been trying to decide between Pfeiffer's bacillus and a filtrable virus (hypothetical at the time) as the cause of that disease.

A Complex Etiology in Swine Influenza. There was one possibility which, if true, would explain the observations: perhaps swine influenza was a disease of complex etiology and both the organism and the virus were essential to its causation. This was tested experimentally by inoculating a pig intranasally with a mixture of *H. influenzae suis* and the virus. It came down with swine influenza. Further experiments were carried out and in these the effect of the virus alone and the organism alone were carefully controlled. The results of 5 such experiments are outlined in table 1.

As shown in table 1, all 8 of the swine infected by inoculation with Berkefeld filtered infectious material or by contact with filtrate-infected swine developed only the mild filtrate disease. In some instances it was so slight as almost to escape recognition. None of the animals exhibited a febrile reaction. Those coming to autopsy showed the scant scattered areas of pulmonary atelectasis characteristic of the filtrate disease.

The swine which were inoculated intranasally with pure cultures of *H. influenzae suis* were completely negative both clinically and at autopsy.

All the swine which received mixtures of the virus and *H. influenzae suis* developed a disease that was typical of swine influenza both clinically and at autopsy. Of the 7 hogs infected either by direct inoculation with the virus-bacterium mixture or by contact with swine so infected, three developed a disease that was of about the same severity as that shown by the control animals inoculated with unfiltered infectious material. Two others had a mild in-

TABLE 1

Effect of inoculating swine with mixtures of swine influenza virus and H. influenzae suis

EXPERIMENT NO.	INFECTIOUS MATERIAL FROM SWINE NO.	SWINE INOCULATED NO.	INOCULATED INTRANASALLY WITH	CLINICAL PICTURE	AUTOPSY FINDINGS	H. INFLUENZAE SUIS IN		REMARKS
						Lung	Bronchial exudate or scrapings	
1	860	859	10 cc. Berkefeld N filtrate	Mild filtrate disease	Very few	Absent	Absent	Illness extremely mild
	Strain 14 (1930)	861	8 cc. Berkefeld N filtrate + 2 cc. culture HIS*	Typical and severe influenza	Typical and extensive	Pure culture	Pure culture	More severe disease than control (871)
	In infusion broth	871	10 cc. unfiltered suspension	Typical influenza	Typical	Pure culture	Mixed culture	Control of unfiltered suspension
2	872	875	4 cc. Berkefeld N filtrate	Mild filtrate disease	Very few	Absent	Absent	Illness extremely mild
	Strain 15 (1930)	874	4 cc. Berkefeld N filtrate + 2.5 cc. culture HIS	Typical influenza	Typical	Pure culture	Mixed culture	Disease about same severity as control (876)
	In infusion broth	873	2.5 cc. culture HIS in 4 cc. infusion broth	No illness	Negative	Absent	Mixed culture	Control of culture alone
		876	4 cc. unfiltered suspension	Typical influenza	Typical	Mixed culture	Pure culture	Control of unfiltered suspension
3	878	894	7 cc. Berkefeld N filtrate + 2 cc. sterile horse blood	Mild filtrate disease	Few	Absent	Absent	Scarcely recognizable illness
	Strain 15 (1930)	897	Infected by contact with Swine 894	Mild filtrate disease	Not autopsied			Scarcely recognizable illness
	In distilled water	892	7 cc. Berkefeld N filtrate + 2 cc. culture HIS	Typical influenza	Typical	Mixed culture	Pure culture	Same severity as disease in control (895)
		896	Infected by contact with Swine 892	Very severe influenza	Typical and extensive	Pure culture	Mixed culture	Moribund when killed
		893	2 cc. culture HIS in 7 cc. distilled water	No illness	Negative	Absent	Mixed culture	Control of culture alone
		895	5 cc. unfiltered suspension mixed with 10 cc. normal swine serum	Typical influenza	Typical	Mixed culture	Not cultured	Control of unfiltered suspension

4	907	911	4 cc. Berkefeld N filtrate	Mild filtrate disease	Few	Sterile	Sterile	Scarcely recognizable illness
	Strain 15 (1930)	910	4 cc. Berkefeld N filtrate + 2 cc. culture HIS	Mild influenza	Typical	Sterile	Mixed culture	Same type of disease as control (913)
	In infusion broth	915	Infected by contact with Swine 910	Mild influenza	Typical	Pure culture	Mixed culture	Same type of disease as control (913)
		912	2 cc. culture HIS in 4 cc. infusion broth	No illness	Negative	Absent	Pure culture	Control of culture alone
		913	4 cc. unfiltered suspension	Mild influenza	Typical but few	Absent	Pure culture	Control of unfiltered suspension
5	918	919	8 cc. Berkefeld N filtrate†	Mild filtrate disease	Not autopsied			Scarcely recognizable illness
	Strain 15 (1930)	920	8 cc. Berkefeld N filtrate	Mild filtrate disease	Not autopsied			Scarcely recognizable illness
		921	8 cc. Berkefeld N filtrate	Mild filtrate disease	Not autopsied			Scarcely recognizable illness
	In infusion broth	923	8 cc. Berkefeld N filtrate + 2 cc. culture HIS	Typical and severe influenza	Typical	Pure culture	Pure culture	More severe than disease of control (951)
		922	2 cc. culture HIS in 8 cc. infusion broth	No illness	Not autopsied			Control of culture alone
		951	8 cc. unfiltered suspension	Typical influenza	Typical	Pure culture	Pure culture	Control of unfiltered suspension

* HIS = *H. influenzae suis.*

† *B. prodigiosus* present in filtrate. *H. influenzae suis*, however, could not be demonstrated. All other filtrates recorded were sterile.

fluenza but the disease which developed in their control was also atypically mild. The remaining 2 swine came down with an influenza of very severe type which exceeded that developed by their controls. These experiments are interpreted to indicate that swine influenza is caused by the concerted action of a filtrable virus and *H. influenzae suis*. The dilemma of too many etiological agents was thus finally solved by accepting both as essential.

The mechanism by which the two agents act in concert to cause influenza is unknown, although several possibilities are apparent. It may be that the pathogenic activities of the virus are such as to create a portal of entry for *H. influenzae suis* and to furnish a favorable medium in which it can multiply. There can be little doubt that, in the presence of swine influenza virus, the organism possesses invasive powers which it completely lacks when administered alone. A second possibility is that the virus is the important component in contributing to the pathology and perhaps also to the symptoms characterizing the clinical picture and that the organism, acting in the fashion of Reynals' factor (9), enhances to a marked degree the pathogenic properties of the virus, and hence the severity of the resulting disease. A third possibility, and one rendered very likely from consideration of the qualitative and quantitative differences between the pathology of the filtrate disease and swine influenza, is that the activities of both the virus and the organism are influenced by the concomitant presence of the other agent in the respiratory tract and that both actually contribute to the lesions of swine influenza.

The question of whether any bacterium other than *H. influenzae suis* can play a primary etiological rôle in swine influenza has not been exhaustively studied. However, in numerous infections of swine with virus alone none of the organisms comprising the normal respiratory tract flora has been capable of acting with the virus to cause the disease. Furthermore, the constant presence of *H. influenzae suis* in experimental infections induced by ten strains of swine influenza collected in the autumns of five different years seems sufficient to indicate that, if not the only bacterium able to complete the etiological complex, it is at least the predominating one for the regions from which our infectious material has been obtained.

A FILTRABLE VIRUS IN HUMAN INFLUENZA

In 1933 Smith, Andrewes, and Laidlaw (10) transmitted a disease to ferrets by inoculating intranasally filtrates of pharyngeal washings from cases of epidemic influenza in man. The ferret disease proved to be serially transmissible, and was characterized by a 2-day incubation period, a diphasic temperature response, symptoms of nasal catarrh, and variable systemic disturbances. The mucous membranes of the nasal passages of ferrets killed during the first or second febrile periods were acutely inflamed. Histological examination revealed vascular congestion, dilated lymph channels, numerous leucocytes, and complete disappearance of ciliated cells. The causative agent possessed the properties of a filtrable virus. In their original work, Smith, Andrewes, and Laidlaw recovered the virus from the throat washings of 5 of 8 cases tested and failed to recover it from 4 subjects not suffering from influenza. Sera obtained from either recovered ferrets or from patients after an attack of influenza neutralized the virus. All the evidence first presented and that obtained later points to the etiological importance of this virus in the disease. A laboratory animal for use in studying human influenza was thus, after so many years, at hand.

Smith, Andrewes, and Laidlaw also found that swine influenza virus was infectious for ferrets and in them produced an illness similar to that caused by the virus of human origin.

The susceptibility of ferrets to swine influenza virus was easily confirmed. However, because difficulty was encountered in administering infectious suspensions intranasally some of my animals were lightly etherized prior to inoculation (11). Ferrets infected in this way developed a more severe illness than that described by the English investigators, exhibiting an extensive bloody, edematous, lobar pneumonia when autopsied on the 4th or 5th day after infection. The pneumonia sometimes terminated fatally. In contrast to influenza in swine, the ferret disease was not modified in character when cultures of *H. influenzae suis* were inoculated together with the virus.

In 1934, Francis recovered a virus from cases of epidemic influenza in Puerto Rico (12). In its earlier passages, this virus pro-

duced a disease in ferrets similar in all respects to that described for the English virus. Francis thus confirmed the observations of Smith, Andrewes, and Laidlaw that a filtrable, infectious agent could be transferred from human cases of epidemic influenza to ferrets. Furthermore, Francis found that after several passages in ferrets anesthetized at the time of inoculation, his virus produced pneumonias similar to those seen in ferrets inoculated in this way with swine virus. He pointed out that this suggested adaptation of the human virus to the ferret. Similar passage of the English strain has since resulted in its also acquiring the ability to produce pulmonary consolidation (13). It is thus apparent, as Francis indicated, that ferret-adapted human influenza virus possesses pathogenic properties for ferrets like those shown from the beginning by swine influenza virus.

THE INFECTION OF MICE WITH INFLUENZA VIRUS

Andrewes, Laidlaw, and Smith (14), and Francis (12) discovered independently that the human influenza virus could be transmitted to white mice after preliminary passage in ferrets.

Mice inoculated intranasally, while etherized, with a mouse-adapted virus, usually showed symptoms within 24 to 48 hours. Their coats appeared staring, they became less active, lost their appetites and remained huddled together in a corner of their cage. Later the illness was characterized by exaggerated respiratory movements, definitely slower than those of normal mice. Some of the animals died as early as the 3rd or 4th day of their illness. The mortality from a heavy dose of virus approached 100 per cent. At postmortem the only constant changes were in the lungs. These were deep red and almost airless except for small emphysematous areas at the periphery. In mice that died all lobes were usually consolidated, while in those killed early in their disease various degrees of lung involvement were seen.

The virus of swine influenza also proved pathogenic for mice and produced a disease in this species which was indistinguishable clinically or pathologically from that caused by the human agent (14). There was, however, one important difference. As mentioned above, the human virus required a preliminary period

of adaptation in the ferret before it could be transferred to mice (15). The swine virus, on the other hand, could be transmitted directly from swine to mice without intervening ferret passage (16). Like the disease in ferrets, that in mice was not modified when *H. influenzae suis* was administered together with the virus.

The discovery of the susceptibility of the mouse to the viruses of human and swine influenza has made possible experimental work that was not feasible when it was necessary to use the more expensive ferrets or swine. Mice have proven especially useful in studying the immunology of the influenza viruses.

IMMUNOLOGICAL RELATIONSHIP BETWEEN THE VIRUSES OF HUMAN AND SWINE INFLUENZA

To date, strains of the human influenza virus obtained from four such widely separated localities as London (10), Puerto Rico (12), Philadelphia (17), and Melbourne (18) have been studied immunologically and found to be identical so far as could be determined (15, 17, 18). Likewise, strains of swine influenza virus obtained in three different epizoötic periods have proved immunologically the same (19). Since the character of the disease produced by the human and swine viruses in ferrets and mice was similar, the question of the antigenic relationship between the two agents arose. Smith, Andrewes, and Laidlaw (13) found that ferrets recovered from infection with either human or swine virus were usually immune to the other. However, though each virus was neutralized by admixture with homologous ferret immune serum, neutralization was inconstant if the heterologous serum was used. Thus, of four human virus-immune ferret sera tested against swine virus in ferrets, two failed to neutralize, one neutralized and the fourth neutralized in one test but failed in another. Of three swine virus-immune ferret sera, one neutralized human virus while the others failed.

Francis and I obtained similar results. We found that mice recovered from infection with either virus were immune to the other (16). However, the sera of animals recovered from infection with the one virus, though capable of neutralizing it, exerted

little, if any, demonstrable protection against the other. Hyper-immunization of animals, especially to the human virus, tended to increase the heterologous neutralizing activity of their sera (20). The conclusion reached was that the viruses were related but not identical.

ANTIBODIES TO HUMAN AND SWINE INFLUENZA VIRUS IN HUMAN SERA

Smith, Andrewes, and Laidlaw (13) showed that the sera of persons convalescent from influenza neutralized the human virus. Francis and Magill (21) demonstrated that these antibodies actually develop during an attack of the disease. Sera of 3 persons, bled during the acute stage of influenza, failed to neutralize human influenza virus, whereas that obtained during their convalescence and again 6 months later did neutralize it. The presence of antibodies against the human virus in the serum of an individual appears, therefore, to be an expression of a previous infection with that virus.

Andrewes informed me in a personal communication that he and his co-workers had found antibodies neutralizing swine virus in high titer in the serum of a human adult and that they proposed further studies to determine how frequently such antibodies might be encountered. About this time Francis and Magill were undertaking a study of the neutralizing antibodies for human virus in sera from individuals of various ages and it seemed opportune, in view of Andrewes' information, to study this same group of sera for their ability to neutralize swine virus. We knew from experience with the sera of animals recovered from infection with either virus that the antibodies developed were quite specific for each type of agent (20). It seemed likely, therefore, that if antibodies neutralizing swine virus were present in human sera they could be detected independently of those effective against the human virus.

The results of the experiments conducted in England and in this country were in close agreement, as shown in table 2.

Andrewes, Laidlaw, and Smith (15), arranging their cases in age groups, found that the sera from 62 per cent of the individuals

over 20 years significantly neutralized the human virus; 100 per cent neutralized the swine virus. In the age group 15 to 19 years 77 per cent neutralized human virus, while here again 100 per cent neutralized swine virus. In the age group 10 to 14 years, 42 per cent neutralized human virus, and those neutralizing swine virus had fallen to 44 per cent. In the group of children under 10 years, 33 per cent neutralized human virus but not a single serum from this group neutralized swine virus. They remarked on the striking fact that, while neutralizing antibodies

TABLE 2

Human and swine influenza virus-neutralizing antibodies in human sera

AGE GROUP	EXPERIMENTS OF ANDREWES, LAIDLAW AND SMITH						EXPERIMENTS ●F FRANCIS, MAGILL AND SHOPE					
	Neutralization ●f Human virus			Neutralization ●f Swine virus			Neutralization of Human virus			Neutralization of Swine virus		
	No. sera tested	Significant neutralization		No. sera tested	Significant neutralization		No. sera tested	Complete neutralization		No. sera tested	Complete neutralization	
		Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
Under 10 years....	15	5	33	14	0	0	33	16	49	27	3	11
10–19 years....	21	12	57	15	10	66	12	7	58	8	5	63
Over 20 years....	29	18	62	19	19	100	80	38	48	77	71	92

for swine influenza virus were present in the sera of all individuals 15 years of age or older, they were completely absent in the sera from children under 10 years of age.

When Francis and Magill's results (22) and my own (23) were considered in age groups similar to those used by the English workers, it was found that the sera from 48 per cent of the individuals over 20 years of age completely neutralized the human virus; 92 per cent neutralized the swine virus. In the age group 10 to 19 years, 58 per cent neutralized human virus, while 63 per cent neutralized swine virus. In the group of children under age

10, but not including newborn infants, 49 per cent neutralized human virus while only 11 per cent neutralized swine virus. The age at which neutralizing antibodies for swine influenza virus were first regularly encountered in our experiments was 12 years, as compared with 10 years in the English experiments. The contrast in the ability of adults' sera and that from children to neutralize the swine virus was, however, almost as striking as that shown by the results of Andrewes, Laidlaw, and Smith. In our experiments serum from only 4 of 31 of those under 12 years of age completely neutralized the swine virus, whereas that from only 6 of 81 of those 12 years of age or older failed to do so.

As already mentioned, the presence of antibodies for the human influenza virus is probably an expression of a previous infection with that virus. An interpretation of the significance of antibodies for swine influenza virus in human sera, however, is more difficult because no strain of influenza virus immunologically identical with the one obtained from swine has been recovered from man. The question will be considered more fully later.

THE SUSCEPTIBILITY OF SWINE TO THE VIRUS OF HUMAN INFLUENZA

Because the pathogenic activities of human and swine influenza virus were similar in ferrets, Elkeles was led to attempt the transmission of the human agent to swine (24). He succeeded in producing a mild illness in very young pigs inoculated intranasally under light ether narcosis. At autopsy these animals sometimes showed scattered dark red bronchopneumonic areas of consolidation in the upper lobes of the lung. When cultures of either the human or swine influenza bacillus were added to the virus at the time of its administration, the swine developed a more severe illness. The clinical picture was characterized by a low-grade fever, apathy, and loss of appetite. At autopsy varying degrees of bronchopneumonia were encountered. Virus pathogenic for ferrets could be recovered from the pneumonic lungs. It thus appeared that Elkeles had produced a disease somewhat resembling swine influenza in pigs by the administration of human virus mixed with influenza bacilli of either human or swine origin.

Francis and I were able to confirm Elkeles' observation that
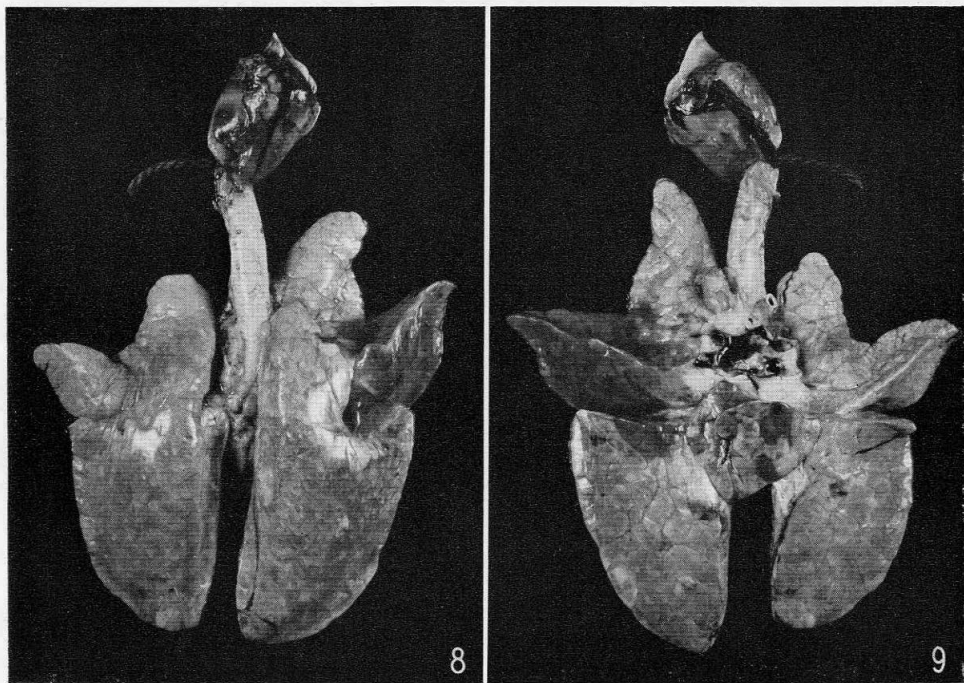
Fig. 8. Dorsal aspect of lung of swine infected with mixture of P. R. 8 strain human influenza virus and *H. influenzae suis*. There is an atelectatic pneumonia of the right cardiac lobe. Animal chloroformed on 3rd day of illness.

Fig. 9. Ventral aspect of same lung. The pneumonia involves all of the right cardiac lobe and lobular areas of the azygos and upper portion of the right diaphragmatic lobes.

swine are susceptible to human influenza virus (19). Unlike Elkeles, however, we did not find it necessary to use very young pigs, nor to anesthetize our animals in order to induce infections, although more extensive pulmonary lesions resulted in swine inoculated while under ether.

The human virus administered intranasally causes a disease in swine that is indistinguishable clinically and pathologically from the mild illness induced by the swine virus alone. When small amounts of the organism *H. influenzae suis* are administered with the human virus a more prostrating febrile illness usually results. This is similar to swine influenza although never so severe. At autopsy the pneumonia encountered is of the same character as that seen in swine influenza but much less extensive; seldom are more than two lobes affected (figures 8 and 9). Involved areas of lung show the same histological features encountered in swine influenza. The lumen of the bronchi are filled with leucocytes (fig. 10), and the bronchial epithelium is fragmented, vacuolated, and denuded of cilia (fig. 11). There is an extensive peribronchial round cell infiltration (fig. 10). The alveolar walls are folded, thickened, and infiltrated with mononuclear cells (fig. 12), and the alveoli themselves contain small numbers of red blood cells and leucocytes. The disease caused in swine by the human virus and *H. influenzae suis* can best be characterized as a mild swine influenza similar qualitatively but differing quantitatively from the typical disease occurring naturally in this species.

Of further interest was the observation that not all pigs inoculated with the human virus and the swine bacterium developed a more severe illness than that caused by the virus alone. Some exhibited symptoms and pulmonary lesions like those seen in the filtrate disease, and in these it could be shown that *H. influenzae suis* had failed to become established with the virus. Instances of this nature have never been encountered in swine inoculated with swine influenza virus and *H. influenzae suis*. The facts would lead one to conclude that, in swine, the human virus possesses less invasive power than does the swine virus. Furthermore, the human virus seems to be inherently less capable of acting synergistically with a second organism than is swine influenza virus.
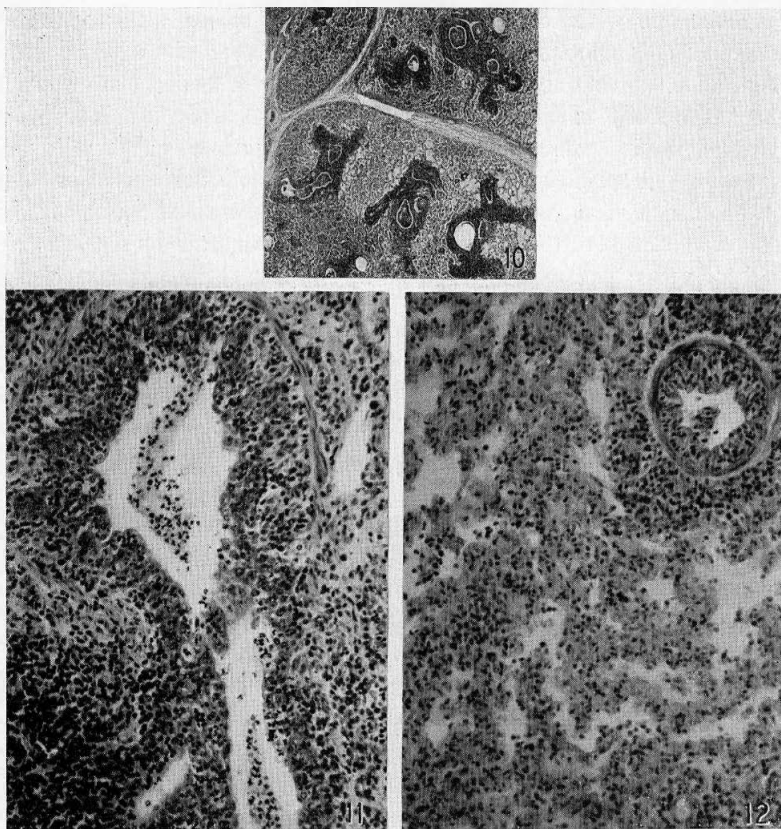
Fig. 10. Section of lung of a swine infected with mixture of P.R. 8 strain human influenza virus and *H. influenzae suis*. The small bronchi contain a leucocytic exudate; there is a dense peribronchial round cell infiltration, the walls of the surrounding alveoli are infiltrated with round cells, and leucocytes may be seen in some of the alveoli. Animal stunned and bled to death on 3rd day following inoculation. Phloxin-methylene blue. × 15.

Fig. 11. Section of a small bronchus in lung of a swine infected with mixture of P.R. 8 strain human influenza virus and *H. influenzae suis* showing leucocytic bronchial exudate, fragmented and vacuolated epithelium denuded of cilia, and round cell infiltration of the submucosa. Leucocytes have invaded the mucosa. Animal chloroformed on 3rd day following inoculation. Phloxin-methylene blue. × 137.

Fig. 12. Section of lung of a swine infected with P.R. 8 strain human influenza virus showing round cell infiltration of the alveolar walls in an area of atelectasis. Animal chloroformed on 3rd day following inoculation. Phloxin-methylene blue. × 137.

Since one of the characteristic features of swine influenza is its extreme contagiousness, we endeavored to determine whether the human virus was also highly communicable in swine. We found that it was not, and that it thus differed significantly in this respect from swine influenza virus. However, the human virus could be transmitted serially in swine by intranasal inoculation of swine of each succeeding passage with virus derived from the lung of the infected animal of the preceding passage. The pathogenic properties of virus transmitted in this way for five serial passages were not altered for either swine or mice; that is, there was no evidence of further adaptation of the virus to swine. Also its immunological identity remained intact.

DISCUSSION

The facts brought out by recent studies of swine and human influenza have been presented. I should like now to discuss these in an effort to point out the possible relationship between the two diseases and to indicate what knowledge, gained by study of swine influenza, may be applicable to the human disease.

As was stated earlier, many middle western veterinarians and farmers were, in 1918, impressed by the similarity between hog flu and the influenza then prevalent in man and suspected that the two conditions might be causally related. Two facts, brought to light early in our experimental work, suggested that these popular suspicions might be correct. The first had to do with the presence of a leukopenia in swine influenza. The second concerned the similarity of the predominant bacterium encountered in swine influenza to that long believed to be the cause or one of the causes of human influenza. The observation that a filtrable virus was etiologically essential in swine influenza, on the other hand, was predicted by no advance information concerning the human disease and it was not until Smith, Andrewes, and Laidlaw recovered a virus from cases of influenza in man that a human agent was available for comparison.

The results of this comparison have been given earlier but require further discussion. The viruses from both swine and man were found to be pathogenic for ferrets, although the human

agent possessed less initial pathogenicity for this species than that from swine. Etherization of ferrets at the time of inoculation enhanced the pneumonia-producing activity of each virus. Both viruses proved fatally pathogenic for white mice except that here a preliminary period of adaptation in the ferret was required for the human but not for the swine virus. It seems likely that these initial differences in the pathogenic activities of the two agents may be those due to "fixation" by prolonged sojourn in a foreign host, since passage of human influenza virus through ferrets alters it in such a way that it becomes more like the swine influenza virus and less like the one originally obtained from man. Human influenza virus, fully adapted to the ferret, produces a clinical and pathological picture in ferrets and mice that is indistinguishable from that caused in these animals by swine virus.

But the similarity does not end here; the two agents are immunologically related. Ferrets, mice, or swine recovered from infection with one virus are usually solidly immune to the other. However, the sera of such immune animals, although neutralizing the homologous virus perfectly, exert as a rule little or no neutralizing action against the heterologous virus.

The facts above demonstrate that the viruses from man and swine, while undoubtedly possessing some antigenic elements in common and producing similar disease manifestations in ferrets and mice, are not identical and can be distinguished from each other immunologically. So far as they go, these data indicate that the swine virus is specific for swine, and that it is different from the one currently prevalent in man.

However, when the sera from human beings were tested for their ability to neutralize the human and swine influenza viruses the results were such as again to focus attention on the possibility that the swine virus had at some time in the past been a human pathogen. It was found, as expected, that sera from many people of all ages neutralized the human virus. It was surprising though to discover that sera from most adults also neutralized the swine virus. We knew from experience with sera of animals immune to either the human or swine agent that the neutralization test was quite accurate in denoting the type involved in previous infections.

There was no reason for supposing that, with human sera, it would be less exact in indicating the type of virus causing previous infections in man. The one disturbing possibility was that in man, as in the case of some animals (20), repeated exposures to human virus might result in the establishment of antibodies effective against both viruses. Comparison of duplicate tests against the two types demonstrated clearly that antibodies neutralizing swine virus were frequently present in human sera that failed to neutralize human virus. In these it was evident that the neutralizing antibodies for swine influenza virus had not resulted from previous infections with human virus. It seemed most probable that their presence indicated a past infection with a virus having an antigenic composition similar to that of swine influenza.

It is apparent from these findings that human sera contain neutralizing antibodies for at least two immunologically distinct types of influenza virus. One is the current human virus of Smith, Andrewes, and Laidlaw known to be widely prevalent in man at the present time. The other, of an antigenic composition similar to swine influenza virus, is unknown and has never been detected in man. It has, however, left ample evidence of its past widespread prevalence in the form of neutralizing antibodies in the sera of almost all adult human beings. That it is no longer widely existent in the human population is indicated not only by the failure of investigators to recover it from cases of influenza during the past two years, but by the almost complete absence of antibodies specific for it in the sera of children under 10 years of age. Unless one wishes to ascribe a non-specific character to the swine virus-neutralizing antibodies in human sera, the conclusion that this unknown human virus was indeed swine influenza virus, or a closely related agent, is inescapable.

However, there is no direct evidence that the swine influenza virus, as we know it today, is capable of infecting man. Indeed, indirect evidence indicates that it does not infect man because, while swine influenza has occurred annually since 1918, our serological evidence suggests that the human prototype of swine influenza virus ceased infecting man generally at least 10 years ago.

The most apparent interpretation of these findings is that the

swine virus represents a surviving form of an extinct or temporarily quiescent human influenza virus and that it has become so "fixed" in swine as to be no longer pathogenic for human beings. If this is the case, then the history that swine influenza appeared for the first time in 1918 serves to date the time of prevalence of this vanished human virus. It is believed that the experimental and historical facts are best explained by the theory that swine influenza virus represents a surviving form of that pandemic in man in 1918, as already suggested by Laidlaw (25), and that it has not had its immunological identity detectably altered by its prolonged sojourn in hogs. On this basis, the presence in human sera of antibodies neutralizing swine virus would be considered to indicate that the donors of these sera had undergone an immunizing exposure to, or infection with, an influenza virus of the 1918 pandemic type.

There can be little doubt that recent human influenza of the type from which Smith, Andrewes, and Laidlaw and Francis recovered their viruses is a benign ailment compared to that rampant in 1918. It might be expected that this difference would be apparent in the character of the disease produced by the two viruses in experimental animals, assuming the swine virus to be representative of the 1918 human type. So far as ferrets and mice are concerned, it is doubtful whether even an experienced observer could certainly differentiate by clinical or postmortem examination between the diseases caused by the two viruses once they are established in these animals. However, in the hog, differences are apparent. If it could be postulated, for the sake of the present discussion, first that swine influenza etiologically is a replica of the human pandemic disease, and second that swine and man react alike to infection with virus and bacterium, then the differences in the behavior of swine and human influenza virus in swine might very well reflect differences between severe pandemic and milder interpandemic human influenza. Under this assumption, two dissimilarities between the swine and human viruses, so far as their behavior in swine is concerned, acquire importance. The first has to do with communicability. The disease caused by the swine influenza virus is highly contagious, while the human

virus is of low communicability. The other concerns the ability
of the two viruses to act synergistically with a second organism.
Swine virus administered in combination with *H. influenzae suis*
causes a prostrating illness, an extensive pneumonia, and the
bacterium always establishes itself in the respiratory tract. The
human virus, on the other hand, given in combination with the
same organism, causes a less prostrating illness, a less extensive
pneumonia and, not infrequently, the bacterium fails to establish
itself along with the virus in the lower respiratory tract. Dif-
ferences such as these in the pathogenic properties of two closely
related agents could readily account for epidemiological and clini-
cal differences in the diseases they caused.

Incidentally, in view of the low communicability in swine of the
strain of human influenza virus recently prevalent, it seems un-
likely that it could establish itself in this species and progress to
cause any widespread or serious epizoötic disease such as the 1918
pandemic virus supposedly did.

Thus far the discussion has concerned mainly the viruses in-
volved in the influenzas of swine and man. What of the rôles
played by bacteria associated with them: *H. influenzae suis* in
the swine disease, and *H. influenzae*, streptococci, pneumococci,
and other organisms, in the human disease? I can speak with
certainty only regarding swine influenza. Here *H. influenzae
suis* must be considered a definite and indispensible part of the
etiological complex: It is always present in the respiratory tracts
of swine ill of the disease; under natural or experimental conditions
it transfers with the virus in series from swine to swine; it can be
substituted by no other known swine pathogen; a disease similar
to the naturally occurring swine influenza results only when it
accompanies the virus in experimental infections; and it enhances
the activity of the virus in a constant and predictable fashion.
I can think of no reason for relegating it to the rôle of secondary
invader unless one wished arbitrarily to consider the mild filtrate
disease caused by the virus alone as true swine influenza and the
natural disease, diagnosed as such in the field, as something else.
There is no evidence to indicate that the filtrate disease exists as a

natural infection of swine or that the virus ever invades swine, under farmyard conditions, unaccompanied by the organism. The similarity of *H. influenzae suis* to *H. influenzae* suggests that, like the swine influenza virus, it may have had its origin in man. Because of the apparent indispensibility of the organism to the virus in causing the disease, it seems most likely that both entered swine at the same time. It would indeed be difficult to conceive that a bacterium, possessing the potential pathogenicity of this organism, should long persist as an unknown saprophyte in swine and acquire recognition only when a low-grade virus happened along to supplement its latent disease-producing capacity.

If *H. influenzae suis* actually did transfer with the virus from man to swine in 1918, and if it is a direct descendant of the *H. influenzae* then prevalent, we must ask why, of all the other organisms known to be involved in human influenza of that time, it alone became established in swine. A possible answer, if one wishes to maintain an analogy between the swine and human diseases, is that pandemic human influenza, like swine influenza, may be a disease of definite complex etiology and swine passage may have served to segregate the two essential etiological components from the assortment of streptococci, pneumococci, and other organisms secondarily involved. Separation and isolation of pathogenic microörganisms from mixtures by inoculation of experimental animals is a well-known and accepted laboratory procedure, and it is reasonable to suppose that it might occur under natural conditions.

However, it may be a mistake to attempt too close a comparison between swine and pandemic human influenza by insisting that *H. influenzae suis* and *H. influenzae* play analogous rôles respectively in the two diseases. It is possible that, in the human disease, any one of a large number of pathogenic microörganisms can act with the virus to cause a severe illness and that, of these, only *H. influenzae* could become established in swine. Thus in 1918, while the human disease may have been caused by the virus in conjunction with pneumococci, streptococci, *H. influenzae* and

other microörganisms, the infections that became established in swine were always those only of the virus and *H. influenzae* because these two agents, of all those involved in the human disease, may have been the only ones suited to an existence in the swine respiratory tract.

A last possibility which must be kept in mind is that human beings may react to infection with influenza virus in the same fashion as ferrets and mice. In this event the virus would be considered the sole and primary etiological agent and the bacteria encountered would be thought of as merely concomitant and of secondary importance. Certainly, were it not for swine influenza with its known complex etiology of virus and bacterium, it seems likely that the recently discovered human influenza virus might now prove entirely acceptable as the sole cause of human influenza on the basis of its pathogenic activities in ferrets and mice. However, the disease caused in ferrets and mice by the human influenza virus may be just as highly artificial in reflecting the complete etiology of human influenza as is that caused in the same animals by swine influenza virus in reflecting the complete etiology of the swine disease. I think it would be a mistake, at this time, to focus all of our attention on this new virus and to neglect further study of the bacteriology of influenza. It seems to me that all of the facts at our disposal point toward the probability that the virus of human influenza, like that of swine influenza, constitutes only a partial etiology of the disease in which it is involved, and that, with respect to the influenza he suffers, man probably resembles the hog more closely than he does the ferret or mouse.

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