THE INCIDENCE OF NEUTRALIZING ANTIBODIES FOR SWINE INFLUENZA VIRUS IN THE SERA OF HUMAN BEINGS OF DIFFERENT AGES

By RICHARD E. SHOPE, M.D.

(From the Department of Animal and Plant Pathology of The Rockefeller Institute for Medical Research, Princeton, N. J.)

(Received for publication, January 14, 1936)

The experiments described in an accompanying paper (1) were conducted in an effort to determine the factors involved in the development of heterologous neutralizing antibodies by various animals, following immunization or infection with the viruses of swine and human influenza. It was found that, while both human and swine influenza viruses were neutralized consistently by their homologous immune sera, the sera from animals convalescent from a single infection with one virus possessed little, if any, neutralizing capacity for the other. Repeated exposures of the animals to either virus, but especially that of human influenza, tended to increase the heterologous neutralizing activity of their sera.

In a second paper (2) the neutralizing action of sera from a group of human subjects of various ages on human influenza virus was reported. The present paper deals with the ability of these same sera to neutralize swine influenza virus, and the results will be compared with those of the preceding paper in an attempt to determine the relation of the swine virus to disease in man.

The strain 15 swine influenza virus was used in all of the present experiments. It was obtained originally through the kindness of Dr. Fred Crow from a case of the swine disease occurring in Iowa in December, 1930. The sources of the human sera employed have been given in the preceding paper. 11 of the 137 sera obtained were tested against human but not swine virus. 2 more sera, found satisfactory for use by the technique of inoculation employed by Francis and Magill (2) proved toxic for mice by the method used in this laboratory. 1 serum was tested against swine but not human influenza virus. The remaining 123 sera were tested for their ability to neutralize both human and swine virus and these

form the basis for the present paper. It is realized that the number of sera studied is small statistically and that gaps exist in certain important age groups.

Neutralization Tests

The neutralization tests were performed as previously described for swine influenza virus (1). The supernatant of a 2 per cent suspension of glycerolated infected mouse lung was used as the source of virus and mixed with an equal amount of each serum to be tested. The period of storage of the mixtures, the method of their administration to mice, and the criteria for judging the neutralizing effect of sera of unknown potency were the same as already described (1). The amount of swine virus administered to each mouse in each serum-virus mixture was sufficient to kill all or most of the control mice within the 6 day period that each test was allowed to run. At the end of 6 days all surviving mice were killed with chloroform, and the extent of their pulmonary lesions recorded. These lesions and those of mice which died earlier were graded from 4+ for lungs exhibiting a complete influenza virus pneumonia, to 0 for those whose lungs were free of influenza lesions. The basis upon which the final result of each test was determined and upon which the degree of protection afforded by each serum was graded has been described in the preceding paper (2). Mice 3 to 5 weeks old and weighing from 10 to 15 gm. were used.

The results of experiments in which human sera were tested for their ability to neutralize swine influenza virus are shown in Table I.

Consideration of the data given in Table I and presented graphically in Text-fig. 1 shows that the sera of infants between the ages of 3 days and 1 month consistently neutralized swine virus. These results are in agreement with those with sera from individuals of the age group of the mothers of the infants and may be explained as probably due to maternal transfer of neutralizing antibodies. The sera of babies from 2 to 9 months of age, on the other hand, failed to neutralize swine influenza virus. 1 of the 14 sera from children between the ages of 1 and 5 years and 2 of the 8 from children 6 to 9 years old neutralized the virus of swine influenza completely or almost completely. Others of these age groups showed evidence of possessing small amounts of neutralizing antibodies and these will be discussed in more detail later. Of 7 sera from children between the ages of 10 and 12 years, 4 neutralized swine influenza virus completely or almost completely. Those from persons in the higher age groups, from 21 years on, with very few exceptions, neutralized the virus of swine influenza. The results of these experiments are in striking agreement with those published recently by Andrewes, Laidlaw, and Smith (3).

The curve in Text-fig. 1 representing the ability of sera from human beings to neutralize swine influenza virus rose steadily with advancing age to reach a peak of 100 per cent for the sera from persons in the 30 to 39 year age group. It de-

TABLE I

Neutralization Tests with Swine Influenza Virus and Sera of Human Beings of Various Ages

Serum No.	Age of donor	Serum-virus mixture administered intranasally to mice				Result
		Pulmonary lesions				
		Mouse No.				
		1	2	3	4	
	days					
1	3	0*	0	0	0	P†
2	4	0	0	2+	0	P
3	5	0	0	0	0	P
4	6	0	2+	0	2+	I
5	6	0	0	0	0	P
6	7	0	0	0	0	P
7	7	0	0	0	0	P
8	8	0	0	0	0	P
9	10	2+	0	0	0	P
10	11	0	0	0	0	P
11	14	0	0	0	0	P
	mos.					
12	1	0	0	0		P
13	1		Toxic			
14	2	3+	3+	2+		NP
15	2					
16	3	4+‡	4+‡	4+‡		NP
17	8	4+‡	4+‡	4+‡	4+‡	NP
18	9	4+	4+	4+		NP
19	9	4+	4+	4+		NP
20	13	2+	3+	2+	3+	NP
21	13½	2+	3+	2+	2+	PP

* 0 = mouse with no detectable influenzal lesions postmortem.

1+ = mouse with influenzal pneumonia involving upwards to ¼ of lung at postmortem.

2+ = mouse with influenzal pneumonia involving from ¼ to ½ of lung at postmortem.

3+ = mouse with influenzal pneumonia involving from ½ to ¾ of lung at postmortem.

4+ = mouse with influenzal pneumonia involving from ¾ to all of lung at postmortem.

† P = complete protection—serum neutralized the virus.

I = incomplete protection—serum exerted considerable neutralizing effect on virus but failed to protect completely.

PP = partial protection—serum exerted slight neutralizing effect on the virus.

NP = no protection—serum failed completely to neutralize the virus.

‡ = mouse died.

TABLE I—*Continued*

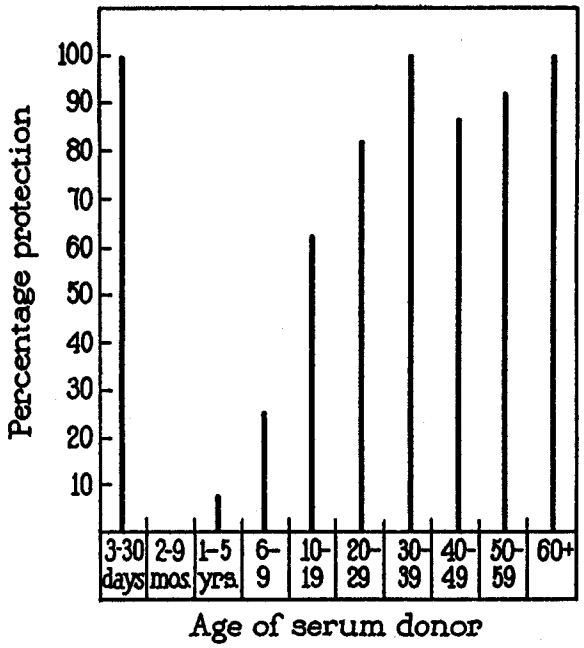
Serum No.	Age of donor	Serum-virus mixture administered intranasally to mice				Result
		Pulmonary lesions				
		Mouse No.				
		1	2	3	4	
	yrs.					
22	1½	4+‡	4+‡	4+‡	4+‡	NP
23	2½	4+‡	4+‡	4+‡	4+‡	NP
24	3	4+‡	4+‡	4+‡	4+‡	NP
25	3	3+	3+	3+	2+	NP
26	3	4+‡	4+‡	4+‡	3+	NP
27	3	2+	0	2+	0	I
28	3	2+	2+	3+	2+	PP
29	3	2+	3+	2+	2+	PP
30	3					
31	3	4+‡	4+‡	2+	4+	NP
32	3	2+	3+	2+	2+	PP
33	4	4+‡	4+‡	4+‡	4+‡	NP
34	5	2+	1+	2+	1+	PP
35	6	1+	0	0	0	P
36	6	4+‡	3+	3+	1+	NP
37	6½	3+	2+	2+		PP
38	7	2+	1+	0	1+	PP
39	7	2+	1+	2+	1+	PP
40	8	2+	2+	1+	2+	PP
41	9	4+‡	4+‡	4+‡	4+	NP
42	9					
43	9	0	0	0	0	P
44	9					
45	10					
46	10	0	1+	0	1+	I
47	10	4+‡	4+‡	4+‡	4+‡	NP
48	11	2+	2+	2+	3+	PP
49	11	3+	3+	3+	2+	NP
50	12	±	0	0	±	I
51	12	0	0	±	0	P
52	12	±	0	1+		I
53	15					
54	18	0	0	0	2+	P
55	18					
56	19					
57	21	4+‡	1+	3+	3+	NP
58	22	0	0	0		P
59	22	0	0	2+	1+	I
60	23	0	0	0	0	P

TABLE I—*Continued*

Serum No.	Age of donor	Serum-virus mixture administered intranasally to mice				Result
		Pulmonary lesions				
		Mouse No.				
		1	2	3	4	
	yrs.					
61	24	±	0	0	1+	I
62	24	0	1+	0	0	P
63	25	0	0	1+	0	P
64	25	0	2+	0	0	P
65	25	0	0	0		P
66	26	1+	1+	0	2+	PP
67	26	±	0	±	1+	PP
68	27	0	0	0	1+	P
69	27	0	1+	0	0	P
70	27	0	0	0	0	P
71	27					
72	28	0	0	0	0	P
73	28	0	1+	±	1+	I
74	28	0	1+	0		I
75	30	1+	0	0	2+	I
76	30	0	0	0	0	P
77	30	0	0	0	0	P
78	30	0	0	0	0	P
79	31	0	0	1+	0	P
80	31	0	0	0	1+	P
81	31	0	0	0	0	P
82	31	0	0	0	0	P
83	31	0	2+	1+		I
84	32	0	±	1+	1+	I
85	32	0	0	0		P
86	32	0	0	0	0	P
87	33	0	0	0		P
88	33	0	0	0		P
89	34	0	0	0	0	P
90	34	0	0	0		P
91	34	0	0	0	0	P
92	34	0	1+	1+	0	I
93	34	0	0	0	1+	P
94	35	0	0	0	0	P
95	36	0	0	0	0	P
96	36	0	0	0		P
97	37	0	0	0	0	P
98	40					
99	42	0	0	0	0	P

TABLE I—*Concluded*

Serum No.	Age of donor	Serum-virus mixture administered intranasally to mice				Result
		Pulmonary lesions				
		Mouse No.				
		1	2	3	4	
	yrs.					
100	42	0	0	0	0	P
101	43	0	0	0	±	P
102	44	0	1+	0	1+	I
103	45	0	1+	2+	0	I
104	45	0	0	0	0	P
105	46	0	0	±		P
106	46	0	0	0	0	P
107	46	0	1+	0	1+	I
108	46	0	0	0	1+	P
109	47	2+	0	1+	0	I
110	47	0	0	0	0	P
111	47	0	0	0		P
112	48	0	2+	2+	±	PP
113	49	2+	1+	1+	1+	PP
114	50	0	0	0	0	P
115	50	0	0	±	0	P
116	50	0	0	0	0	P
117	51	1+	1+	0	0	I
118	52	0	0	1+	0	P
119	52	0	0	0	0	P
120	53	0	1+	0	0	P
121	53	0	0	0	0	P
122	54	0	0	0		P
123	56	0	0	0	0	P
124	57	0	0	0		P
125	58					
126	58	0	0	0	1+	P
127	59	2+	1+	1+	2+	PP
128	60	0	0	0		P
129	60	0	0	0	0	P
130	64	0	0	2+	0	P
131	65	0	0	0		P
132	65	0	0	0	0	P
133	66	0	0	0	0	P
134	70	0	2+	0	0	P
135	70+	0	0	0	0	P
136	73		Toxic			
137	76	1+	0	0	0	P



TEXT-FIG. 1. Percentage of persons of various ages whose sera neutralize the virus of swine influenza. For the purposes of this chart sera which give incomplete (see Table I) as well as complete protection are included.

Protection	Severity of pulmonary lesions (mice)	Age of serum donor									
		3-30 days	2-9 mos.	1-5 yrs.	6-9	10-19	20-29	30-39	40-49	50-59	60+
None	+++		••	••	•	•					
	++		•	••	•	•	•				
Partial	++			••	••	•				•	
	+			•	•		••		••		
Incomplete	±	•		•		••	••	••	••	•	
Complete	0	••• ••• ••• ••			••	••	••• ••• •••	••• ••• ••• ••• ••• ••• ••	••• ••• •••	••• ••• ••• ••	••• ••• •••

TEXT-FIG. 2. Degree of neutralizing activity of sera from persons of various ages for swine influenza virus in mice. Each dot represents a virus neutralization test with serum from one person.

clined slightly in age groups of the next two decades but this is of doubtful significance, since the 3 sera responsible for the decline all partially neutralized the virus.

Text-fig. 2 shows the neutralizing activity for swine influenza virus of sera from persons in the various age groups. The results recorded below the double line have been included in Text-fig. 1 and need no further discussion. Those above the double line represent results with human sera that either failed to neutralize swine virus or neutralized it only partially. The chart shows that most of the non-neutralizing sera were from persons less than 20 years of age. The serum of only 1 person above 20 years of age failed completely to neutralize the virus, while 5 others are recorded as partially neutralizing it.

Correlation of Past History of Influenza with Presence of Swine Influenza Virus-Neutralizing Antibodies

74 persons over the age of 12 years recorded in Table I were questioned as to their past influenza history. The sera of 44 out of 45 (97.7 per cent) of those giving a positive history of influenza neutralized the virus of swine influenza. 17 of those possessing a neutralizing serum gave as the date of their illness a time between 1918 and 1923, 12 between 1930 and 1935, and 5 had influenza both in 1918 and early in 1930. 10 were certain of having had an attack of influenza but were indefinite concerning the date; the 1 person giving a history of influenza whose serum failed to neutralize the virus of swine influenza fell in this group. 29 persons stated that to the best of their knowledge they had never had influenza. The sera of 25 of these (86.2 per cent), however, neutralized swine virus. Since it is realized that histories of influenza outside of pandemic periods are not accurate, the figures outlined above are believed to be of little significance.

Correlation of Age of Serum Donor with the Presence of Neutralizing Antibodies for Swine Influenza Virus

Of the individuals recorded in Table I, excepting the infants 1 month of age or younger, the sera of only 4 of 31 of those under 12 years of age neutralized the swine virus, whereas only 6 of 81 of those 12 years of age or older failed to do so. The possible significance of the correlation between age and the possession of neutralizing antibodies for swine influenza virus will be considered later. It is of interest that Andrewes, Laidlaw, and Smith (3), in their neutralization tests with English sera and swine virus found that none of their sera from persons under 10 years of age neutralized the virus.

Comparison of the Ability of Human Sera to Neutralize the Viruses of Human and Swine Influenza

There can be no doubt from the work of Smith, Andrewes, and Laidlaw (4) that the sera of persons convalescent from influenza neutralize their strains of the human virus. The value of the neutralization test as an indicator of the type of virus involved in previous human infections is suggested by its specificity in animal infections of known type (1, 4, 5, 6). However, it remained for Francis and Magill (7) to demonstrate conclusively that man actually develops antibodies neutralizing human virus following an attack of the disease. They found that the sera of 3 persons, bled during the acute stage of an attack of influenza, failed to neutralize the P. R. 8 strain of the virus of human influenza, whereas that obtained during their convalescence and again 6 months later did neutralize the virus.

The presence of antibodies in human sera capable of neutralizing swine influenza virus is more difficult to interpret because no strain of influenza virus, immunologically identical with that obtained from swine, has been recovered from man. A possible explanation for the presence of these antibodies in such a large proportion of the adult sera examined is afforded by the experiments recorded in the first paper of this series (1). It was shown that while serum of animals convalescent from a single infection with the virus of human influenza possessed little, if any, ability to neutralize swine virus, serum from animals submitted to repeated exposures to human virus was capable of partially or completely neutralizing swine virus. These findings suggested the possibility that the neutralizing properties of human sera for swine virus might be the result of repeated exposures to the virus of human influenza. The fact that sera from adults neutralized swine virus much more frequently than that from children was in accord with this possibility; conceivably the more advanced the age of the person the more numerous had been his opportunities for exposure to the virus of the human disease. The results of the neutralization test with swine virus alone are not sufficient to exclude this possibility. However, when the results of duplicate neutralization tests against the viruses of both human and swine influenza were compared, it was evident that, in a number of instances at least, neutralization of swine virus could not be considered the result of repeated exposures to the

human virus. The sera from 35 persons in the group studied neutralized the swine virus completely but failed to neutralize that of human influenza (see Table II). If, in these 35 cases, the ability to neutralize swine virus had been the result of repeated infections with the virus of human influenza, it would be anticipated that the latter virus would have been neutralized also by the sera. The facts lead one to ask whether the human donors of sera which neutralized swine virus only had not undergone a previous infection with a virus of this sort.

The results obtained in the present study of swine virus have been compared with those described by Francis and Magill (2) for human virus, in order better to evaluate their significance. This comparison is outlined in Table II. An interpretation of the findings, on the basis of the cross-neutralization experiments with sera from animals known to be immune to swine or human influenza virus (1), is also included.

As will be seen in Table II, the sera from only 9 persons, all under 7 years of age (group 1), failed entirely to neutralize either human or swine influenza virus. The sera from 6 persons (group 2), all under 12 years of age, neutralized the virus of human influenza but not that of swine influenza. The sera of another group of 5 persons (group 3), all under 8 years of age, neutralized human virus completely and also exerted a slight neutralizing effect upon swine virus. The sera from 11 persons (group 4), all, with the exception of one new-born, over 24 years of age, neutralized the virus of swine influenza but not that of human influenza. The sera from another group of 24 persons (group 5) neutralized swine virus completely and also exerted a slight neutralizing effect on human virus. 18 of the members of this group were over 24 years of age, 4 were new-born, and the remaining 2 were 6 and 12 years of age.

The sera of 33 persons, listed in Table II as group 6, completely neutralized the viruses of both human and swine influenza. With the exception of 5 new-born and 1 child 9 years old, all of this group were 18 years of age or older. The general age distribution was thus the same as for those listed in groups 4 and 5 whose sera had neutralized only swine influenza virus. The sera of 9 persons, designated as group 7 in Table II, neutralized human influenza virus completely and also exerted considerable neutralizing effect on swine virus, while the sera of 4 others, designated as group 8, neutralized swine virus com-

TABLE II

A Comparison of the Ability of Sera from Human Beings to Neutralize the Viruses of Human and Swine Influenza

Designation group	Degree of protection conferred by sera against each influenza virus		Age of serum donors										Comment and interpretation
			3–30 days	2–9 mos.	1–9 yrs.	10–19 yrs.	20–29 yrs.	30–39 yrs.	40–49 yrs.	50–59 yrs.	60–69 yrs.	70+ yrs.	Totals	Type of virus involved in past influenza infections as judged by results of virus neutralization tests
	Human virus	Swine virus	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.		
1	NP*	NP	0	4	5	0	0	0	0	0	0	0	9	No past influenza infections
2	P	NP	0	1	4	1	0	0	0	0	0	0	6	Past influenza infections with human influenza (PR 8 type) virus
3	P	PP	0	0	5	0	0	0	0	0	0	0	5	
4	NP	P	1	0	0	0	1	2	2	3	1	1	11	Past influenza infections with swine influenza (strain 15 type) virus
5	PP	P	4	0	1	1	2	6	4	3	3	0	24	
6	P	P	5	0	1	1	7	10	2	4	1	2	33	Past influenza infections with both human and swine influenza viruses—or cross-immunity†
7	P	I	1	0	1	2	1	1	2	1	0	0	9	Past influenza infections with human influenza virus and waning immunity to swine influenza virus—or cross-immunity
8	I	P	0	0	0	0	0	1	1	1	1	0	4	Past influenza infections with swine influenza virus and waning immunity to human influenza virus—or cross immunity
9	I or PP	I or PP	1	0	2	1	3	3	3	0	0	0	13	Past influenza infections with either or both swine and human influenza viruses with waning immunity—or previous infection with one related but not identical to either type of virus
10	NP	I or PP	0	0	2	1	1	0	1	1	0	0	6	
11	I or PP	NP	0	0	1	1	1	0	0	0	0	0	3	
Totals.....			12	5	22	8	16	23	15	13	6	3	123	

* NP = no protection. PP = partial protection.
I = incomplete protection. P = complete protection.
These symbols are fully explained under Table I.

† Repeated exposures of animals to either virus, but especially that of human influenza, increase the heterologous neutralizing activity of their sera (1).

pletely and exerted considerable neutralizing effect on human virus. The sera from persons in the last three groups in Table II neutralized neither virus completely, but did partially protect against one or both of them.

The comments on the possible significance of these data in indicating the type of virus involved in past influenzal infections of the persons studied, made in the last column of Table II, are self-explanatory. It is clear that antibodies neutralizing swine influenza virus are present in human sera and frequently independent of those effective against the human virus. The most evident explanation of their presence is that they arose as a result of previous infection by a virus whose antigenic composition was similar to that of swine influenza. The high incidence of swine virus-neutralizing antibodies in sera from adults and their rarity in sera from children further suggest that the agent responsible for their generation has not recently been widely prevalent. This will be more fully discussed later.

DISCUSSION

So far as the present studies are concerned, it has been found that the sera from a very high proportion of human adults neutralize swine influenza virus while those from children below the age of 12, with the exception of new-born infants, seldom exert such an effect. On the surface, the situation would appear to be similar to that known for diphtheria, for instance, in which the serum antitoxin titer, low in childhood, increases with advancing age. To be entirely comparable, however, the causative agent, namely an influenza virus of an antigenic composition similar to swine virus, should be rather widespread throughout the human population. The viruses isolated from clinical cases of influenza in man during the past 2 years from such widely separated localities as London (5), Puerto Rico (9), Philadelphia (6), and Melbourne (10), are immunologically identical (3, 6, 10). Since the human virus differs immunologically from the swine virus (1, 3, 4, 6), its presence cannot be held accountable for the high incidence of antibodies for swine influenza virus encountered in sera from human adults. Moreover, as has been pointed out earlier, the presence of such antibodies cannot be considered the result of repeated exposures to the current human type of virus, because the sera from 35 of the

individuals studied neutralized swine virus but not human virus. It seems unlikely that the age distribution of antibodies neutralizing swine influenza virus can be interpreted on the basis of frequency of opportunity for infection with a virus that is at present widely prevalent. Furthermore, the age distribution of antibodies found by Francis and Magill (2) for an influenza virus of human type known to be prevalent in man during the past 2 years is quite different from that for the virus of swine influenza.

The history of swine influenza furnishes a clue to the interpretation of the neutralization experiments under discussion. The disease was first recognized as a clinical entity in the late summer or fall of 1918.[1] Conversations with veterinary practitioners in eastern Iowa have revealed that the disease caused serious losses among swine on exhibition at the Cedar Rapids Swine Show held from September 30 to October 5, 1918. At the conclusion of the show, the swine, many of them ill, were returned to their home farms and, within 2 or 3 days of their return, influenza was stated to be rampant in the portion of the drove that had remained at home. Shortly thereafter the disease became widespread among swine herds in Iowa and other parts of the Middle West. It persisted in various localities until January of 1919. The epizootic in the autumn and winter of 1919 was stated to be as extensive and severe as that in 1918. The disease has appeared among swine in the Middle West every year since but varies from year to year in its severity and extent.

According to Dorset, McBryde, and Niles (11), 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

[1] Dr. Grant B. Munger of Cedar Rapids, Iowa, has stated in a personal communication that he observed herds of swine ill with influenza as early as August of 1918 in western Illinois where he was then serving as an inspector in the Division of Hog Cholera Control of the Bureau of Animal Industry.

epizootic disease, not seen before 1918, was shared by many veterinary practitioners in the Middle West. Dimoch, in an exhaustive paper on the differential diagnosis of diseases of swine (12) presented in August, 1918, makes no mention of a disease of swine bearing any resemblance to influenza. It seems clear that swine influenza appeared in the Middle West as an epizootic disease for the first time, in recent years at least, during the late summer or early autumn of 1918.

The new disease thus made its first appearance at a time when human pandemic influenza was at its height in the Middle West. Many thought that the two diseases were connected and that swine might have been infected in the first instance from human beings (13). Murray and Biester (14) have called attention to the similarity existing between the "water logged" lung of the human influenzal pneumonia of 1918 and that of the pneumonia of fatal swine influenza. The writer, in earlier work (15), was impressed not only by similarities between the clinical and pathological pictures of human and swine influenza but by the association of a leucopenia with both diseases and, most especially, by the similarity of the predominant bacterium encountered in each disease: *H. influenzae* in the epidemic disease of man and *H. influenzae suis* in the epizootic disease of swine. On the basis of the similarities between the two diseases, after establishment of the fact that swine influenza was caused by the combined action of a filtrable virus and *H. influenzae suis*, it was suggested that an investigation of the possibility that Pfeiffer's bacillus and a filtrable agent act in concert to cause influenza in man seemed indicated. The possibility received support from the discovery by Smith, Andrewes, and Laidlaw (5) of a virus in cases of human influenza similar to that etiologically important in swine influenza, and Laidlaw (16) propounded the view that "the virus of swine influenza is really the virus of the great pandemic of 1918, adapted to the pig and persisting in that species ever since."

The ability of such a large proportion of the sera from human adults to neutralize the virus of swine influenza adds weight to the view that this virus or one of its antigenic composition has recently been widely prevalent in man. The similarity of swine influenza virus to that etiologically important in recent influenza in man, with regard to its pathogenic activity in common experimental animals (5, 8, 9, 17, 18),

further suggests that its past activity, so far as man may be concerned, lay in the production of influenza.

All of these facts viewed as a whole make it necessary to consider seriously the theory that swine influenza virus represents a surviving form of the human pandemic virus of 1918, and that it has not had its immunological identity detectably altered by its prolonged sojourn in hogs. On the basis of this assumption the presence in human sera of antibodies neutralizing the swine virus would be considered as indicating that the donors of these sera had undergone an immunizing exposure to or infection with an influenza virus of the 1918 pandemic type.

Andrewes, Laidlaw, and Smith (3) in interpreting the significance of their neutralization experiments with human sera obtained in England, and the same strain of swine virus used in the present experiments (strain 15, Iowa, 1930) have guardedly suggested an explanation similar to that just outlined. They have qualified their interpretation by considering the possibility that the antibodies to swine virus in adult human sera may be non-specific in the sense that they represent past contact, not with that virus, but with some unknown related antigen.

If swine influenza virus is actually a surviving form of the 1918 human pandemic strain, then two inferences, interesting from an epidemiological standpoint, become apparent immediately. The first of these is that virus of the 1918 type has been present in human beings within the past 6 years, since the serum from one 6 year old child in the group tested neutralized the swine virus. The second is that persons at present susceptible to virus of the 1918 type, as indicated by the failure of their sera to neutralize swine influenza virus, are limited largely to those in the lower age groups born since pandemic influenza ceased to be prevalent.

SUMMARY

Sera from a very high proportion of the human adults and new-born infants studied neutralized swine influenza virus; sera from children below the age of 12 years seldom exerted such an effect. The results of neutralization experiments with human sera and the virus of swine influenza have been compared with the outcome of similar tests with

the virus of human influenza, and it seems evident that the presence of antibodies neutralizing swine influenza virus cannot be deemed the result of repeated exposures to the current human type of virus. From the known history of swine influenza and the similarity of its etiologic virus to that obtained from man it seems likely that the virus of swine influenza is the surviving prototype of the agent primarily responsible for the great human pandemic of 1918, as Laidlaw has already suggested. The presence in human sera of antibodies neutralizing swine influenza virus is believed to indicate a previous immunizing exposure to, or infection with, an influenza virus of the 1918 type.

BIBLIOGRAPHY

1. Francis, T., Jr., and Shope, R. E., *J. Exp. Med.*, 1936, **63**, 645.
2. Francis, T., Jr., and Magill, T. P., *J. Exp. Med.*, 1936, **63**, 655.
3. Andrewes, C. H., Laidlaw, P. P., and Smith, W., *Brit. J. Exp. Path.*, 1935, **16**, 566.
4. Smith, W., Andrewes, C. H., and Laidlaw, P. P., *Brit. J. Exp. Path.*, 1935, **16**, 291.
5. Smith, W., Andrewes, C. H., and Laidlaw, P. P., *Lancet*, 1933, **2**, 66.
6. Francis, T., Jr., *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 1172.
7. Francis, T., Jr., and Magill, T. P., *J. Exp. Med.*, 1935, **62**, 505.
8. Shope, R. E., *J. Exp. Med.*, 1935, **62**, 561.
9. Francis, T., Jr., *Science*, 1934, **80**, 457.
10. Burnet, F. M., *Med. J. Australia*, 1935, **2**, 651.
11. Dorset, M., McBryde, C. N., and Niles, W. B., *J. Am. Vet. Med. Assn.*, 1922–23, **62**, 162.
12. Dimoch, W. W., *J. Am. Vet. Med. Assn.*, 1918–19, **54**, 321.
13. McBryde, C. N., *J. Am. Vet. Med. Assn.*, 1927, **71**, 368.
14. Murray, C., and Biester, H. E., *J. Am. Vet. Med. Assn.*, 1930, **76**, 349.
15. Shope, R. E., *J. Exp. Med.*, 1931, **54**, 373.
16. Laidlaw, P. P., *Lancet*, 1935, **1**, 118.
17. Andrewes, C. H., Laidlaw, P. P., and Smith, W., *Lancet*, 1934, **2**, 859.
18. Shope, R. E., *J. Exp. Med.*, 1934, **60**, 49.