SWINE INFLUENZA

I. Experimental Transmission and Pathology

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Plates 32 to 34

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Swine influenza ("hog flu") was first recognized as a clinical entity in the fall of 1918. Because of the prevalence at the same time of human influenza and a marked resemblance in the symptoms of the two diseases Koen became convinced that they were the same. He therefore gave the name of "flu" to the new malady of hogs (1).

The cardinal features of swine influenza are amply presented in the veterinary literature (1–6).

Swine influenza is essentially a disease of autumn and early winter and reaches epizootic proportions each year. The onset is sudden and the incidence in an affected herd is practically 100 per cent. Fever, anorexia, prostration of an extreme type, cough, and a 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. The period of illness is short, varying from 2 to 6 days, and in uncomplicated cases the recovery is almost as sudden as the onset. The mortality is stated to range from 1 to 4 per cent. Fatal cases exhibit an extremely edematous type of bronchopneumonia.

During the autumn of 1928 and of 1929 two epizootics were observed by the writer in eastern Iowa.[1] That in 1928 was very severe,

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and while the mortality as a whole probably did not exceed 4 per cent, in some herds the losses were more than 10 per cent. In 1929 the epizootic was extremely mild and the mortality was less than 1 per cent.

The term "hog flu," as popularly used, embraces more than one clinical entity. This point was particularly emphasized by our 1929 field observations. While in 1928 the epizootic disease was so plentiful in eastern Iowa that material from typical cases was easily obtained, in 1929 much difficulty was encountered. Many cases were then seen in which a loose diagnosis of "hog flu" had been made. These animals, as a rule, were found to be suffering from a respiratory affection, quite often simulating the true epizootic swine influenza in some respects but differing markedly in others. The true nature of the condition could usually be recognized by the absence of prostration on the part of the affected animals, the greater chronicity of the disease, and the failure of more than a small portion of the herd to become affected.

Experimental Transmission

Swine influenza has been established without difficulty by experimental infection of swine with eight separate strains of the disease brought from Iowa.

Infectious material was transported in tubes packed in iced thermos jugs and was usually *en route* for from 36 to 48 hours. The method used in inducing infections was that described by McBryde, Niles, and Moskey (6). It consisted in the intranasal instillation of either suspensions of bronchial mucus alone or mixtures of suspensions of bronchial mucus, bronchial lymph nodes, and diseased lung. The instillations were made with a Luer syringe without needle by pressing the tip of the syringe into the external nares. The suspensions were prepared in either distilled water or infusion broth and were made up to between 10 and 20 per cent. The dosage of suspension administered usually ranged from 5 to 30 cc., but typical and severe influenza was produced by the intranasal injection of doses as small as 1 cc. Only a small portion of the material administered was retained, for most of it was either sneezed or blown out of the nostrils.

After the establishment of the disease animals from which material for further inoculations was to be taken were slaughtered on the 3rd or 4th day following the first appearance of a temperature in excess of 40°C. The disease has been maintained for study by this type of serial passage.

Because of the highly contagious nature of the disease it has been necessary

to exercise extreme precaution in the isolation of individual experimental animals. Our individual isolation units have been used. We have followed the technique of isolation used here for the study of experimental hog cholera. This practice has been tested repeatedly for both hog cholera and swine influenza and found sufficient to insure complete isolation.

Unlike McBryde and his coworkers (6) we have encountered no spontaneously immune animals during the investigation. The probable explanation is that McBryde investigated the disease during the epizootic period in Iowa and used as his experimental animals swine from the same region. These animals may have been in contact with the disease prior to their use experimentally and may in consequence have developed some degree of immunity. Such a possibility was eliminated in our own experiments. All of the transmission work was conducted at Princeton, New Jersey, and the experimental animals were either raised on the Institute farm or purchased from nearby farmers. Epizootic swine influenza does not occur in the locality.

The method of inoculation has been adequately controlled. Normal swine have been injected intranasally with large doses of suspensions of lung and bronchial lymph nodes from normal swine and in no instance has any evidence of illness developed or anything suggestive of influenzal disease been encountered at autopsy.

Clinical Features of Experimental Swine Influenza

The symptoms induced by the several strains of swine influenza have varied in degree but very little in type.

Strain 1 (1928) induced a more severe and virulent swine influenza than Strain 2 (1928) and Strain 2 in turn was more virulent than Strains 5, 6, 7, and 10 (1929). Strains 14 and 15 (1930) induced a disease which was of about the same severity as that induced by Strain 1. The actual mortality of the experimental disease was not determined, for most of the experimental swine were killed on the 2nd to 4th day of fever for bacteriological and pathological studies. However, fatal infections resulted five times following infection with Strain 1, four times following infection with Strain 14, and six times following infection with Strain 15. The mortality can be safely estimated as higher than that in the naturally occurring field disease.

The incubation period was found to be short. For animals infected by pen contact it varied from 2 to 7 days with the average at 4 days. Animals infected by intranasal instillation became ill more promptly and usually within 24 to 48 hours exhibited a sharp rise in temperature.

Fever, *i.e.*, a temperature of 40°C. or higher, was in all cases the first observable evidence of illness. Accompanying the rise in temperature, or following it very shortly, there was a mild degree of malaise, mild anorexia, and a tendency for the animal to tire easily when made to exert itself. While there was considerable variation in the temperature reaction, as a rule on the 1st day it reached 40.4°C. but seldom exceeded 41°C. On the 2nd day of illness the fever, anorexia, and malaise were more marked. By the 3rd day the temperature had as a rule reached its peak and frequently exceeded 41.5°C. and sometimes even 42°C. At this time respiratory involvement was manifested by increased rate and a peculiar type of diaphragmatic breathing, described popularly as "thumping," and frequently a paroxysmal type of cough was elicited when the animals were roused. They exhibited marked prostration, refused food, and lay listlessly in their pens. Their

TABLE I

Leucocytic Reaction in Experimental Swine Influenza

Swine No.	Before inoculation	Days after inoculation				
		2	3	4	5	6
	Leucocytes per c.mm.	Leucocytes per c.mm.	Leucocytes per c.mm.	Leucocytes per c.mm.	Leucocytes per c.mm.	Leucocytes per c.mm.
459	28,000	24,200	22,000	13,300		
461	19,000	14,000	10,800	12,040		
549	24,400		13,400	14,600	7,400	
555	23,000	17,900	17,300	19,800		21,400
562	28,800	27,600	20,300		11,400	
572	22,600	15,540		11,840		14,200
583	21,920		17,600		15,500	
587	14,940		9,240		13,400	

condition on the 4th and 5th days was little altered from that on the 3rd day. Death occurred on the 3rd, 4th, 5th, or 6th days and was preceded by an exaggeration of all respiratory symptoms, an increase in the prostration, and the onset of an active, incoordinated delirium during which the animal lay on its side and made running motions with its legs or, attempting to stand, would stagger about the isolation unit. On the 6th day as a rule, the temperature was definitely receding in animals that were to recover and from then on recovery was rapid.

In both the natural and the experimental disease a mild leucopenia was usually observed. A record of a few counts on experimental cases is given in Table I. There was no significant difference in the degree of leucopenia of the various cellular types as shown by differential counts.

Pathology

Descriptions of the lesions of swine influenza are fragmentary and deal entirely with fatal cases of the disease.

Dreher (5) has reported the main features as congestion of the mucous membranes of the respiratory tract, a lobular type of pneumonia, swollen and edematous bronchial lymph nodes, and congestion of the gastric mucosa. Dimock and Healy (3) have described the lungs as congested, edematous, fully distended and heavy, and frequently exhibiting bronchopneumonia. Quinn (1) has emphasized the occurrence of extensive edema of the lungs and Murray and Biester (7) found edema to be frequent. The latter authors also called attention to the similarity existing between the "water logged" lung of the human influenzal pneumonia of 1918 and that of the pneumonia of swine influenza.

It has seemed important to study the lesions at various stages of the illness. The large majority of the animals sacrificed would have progressed to an uneventful recovery. The findings in fatal cases will be described separately.

Gross Pathology.—The swine were sacrificed on the 1st to the 5th day of fever. The large majority were chloroformed while a few were stunned by a blow on the head and then bled to death. There were no external signs of disease at the time of slaughter save in some of the animals which seemed most ill. These sometimes exhibited a watery mucous nasal discharge.

The mucosa of the pharynx and larynx was, as a rule, very mildly hyperemic and covered by a white, glassy, tenacious mucus. On opening the trachea the same type of tenacious mucus was present in from moderate to copious amounts. It was sometimes frothy, very rarely blood-tinged. There was more exudate present in the large bronchi and, in the smaller bronchi and bronchioles, it completely filled the lumen. In the bronchioles the exudate was of firmer consistency than higher in the respiratory tract. It not infrequently could be removed in small, white, semitranslucent, sago-like masses. The pleural sacs were free of excess fluid or fibrin. The lungs presented very constant and characteristic gross changes. The involved lung tissue was a deep purplish red in color, noticeably depressed when compared with the uninvolved lung tissue, and the line of demarcation between normal and pathological lung substance was very definite. Palpation of the involved lung revealed that it felt "leathery," did not crepitate, and contained no areas of consolidation. The elements of the bronchial tree could be palpated and gave the impression of being thickened. On cut section the bronchioles protruded from the surface and the lung substance itself had a purplish red, "beefy," pasty appearance throughout. The gross picture was that of a

marked massive atelectasis, irregular both as to amount and distribution. It was usually limited to portions of the cephalic, cardiac, and azygos lobes, and it not infrequently involved all five of these lobes. In over half of the cases it was bilateral and irregularly symmetrical. If, however, it tended to be unilateral, the right side was almost always predominantly involved. There were a number of cases in which only the right cephalic and the cardiac lobe exhibited massive atelectasis. An illustration of a typical case is presented in Figs. 1 and 2.

The adjoining non-atelectatic portions of the lungs were emphysematous. The surfaces of these portions of the lung were elevated and extremely pale. A feature occasionally observed was a moderate to extreme petechiation of the pleurae overlying the areas of compensatory emphysema. In some cases a moderate interlobular edema of the non-atelectatic areas of lung was encountered.

The cervical, mediastinal, and mesenteric lymph nodes were extremely enlarged and very edematous. They were only rarely congested. Those at the hilum of the lung were sometimes so large as to resemble grapes. On section they were found to be soft and to ooze fluid in relatively large amount.

A small excess of fluid was not infrequently encountered in the peritoneum. This was as a rule clear and straw-colored but sometimes slightly cloudy and contained flecks and strands of fibrin. There was usually, but not invariably, a moderate acute splenic tumor. The kidneys and liver were negative in the gross. The stomach was sometimes found to contain a bile-tinged watery mucus and the gastric mucosa was almost invariably extremely hyperemic especially along the greater curvature and at the cardiac end. The small intestine was negative.

The mucosa of the colon frequently exhibited hyperemic patches of various sizes. These areas were mildly edematous and overlaid by a scant catarrhal exudate. They never showed a true fibrinous membrane nor were they eroded. The mucosa was elevated over localized areas of submucous lymphoid hyperplasia.

Histopathology.—

Films of bronchial exudate stained for 24 hours in methylene blue revealed a rather constant and characteristic picture. The predominant cell in the exudate was the polymorphonuclear leucocyte and of these there were many. They were as a rule well preserved and not infrequently contained engulfed organisms, usually small thin bacilli but occasionally larger bacillary forms or cocci. There were moderate numbers of lymphocytes in the exudate and smaller numbers of desquamated epithelial cells. Lying between the cells of the exudate were large numbers of extremely thin, very faintly staining, hair-like structures, evidently broken off cilia. In some preparations these were extremely numerous. Organisms of the type seen in the leucocytes were sometimes very numerous between the cells of the exudate but as a rule they were scarce.

Tracheal sections showed little that appeared abnormal.

Lung sections cut in such a way as to include small bronchi and terminal bronchioles, and including uninvolved and typically diseased lung exhibited the fol-

lowing features. The small bronchi and terminal bronchioles were filled with a polymorphonuclear leucocytic exudate (Figs. 7 and 8). Bacteria were never numerous in this exudate and frequently they were not demonstrable, or were present in such small numbers as to require careful search to find them. They were most numerous at the junction of the exudate and the bronchial epithelium. The cilia lining the smaller bronchi were either entirely gone or badly matted together. The lining epithelium was fragmented, in places partially desquamated, and the cytoplasm of many of the cells appeared vacuolated (Figs. 4 and 5). In the spaces created by the fragmentation of the lining epithelium, leucocytes, singly or in clumps, were sometimes seen (Fig. 5). There was an extensive peribronchial round cell infiltration (Figs. 4, 5, 7, 8). The areas of lung that appeared to be merely atelectatic were found histologically to present other changes than atelectasis alone (Figs. 9 and 10). They were of lobular distribution, and sharply demarcated from adjacent uninvolved lung by interlobular septa, although a number of adjacent lobules might be, and usually were, involved. In these areas the alveoli were collapsed and frequently contained desquamated epithelial cells, small numbers of mononuclear wandering cells, and occasionally some coagulated plasma. Large, feebly stained cells exhibiting a "foamy" cytoplasm were especially numerous in some sections. Leucocytes and red cells were not found regularly in the alveoli although it was difficult to find sections, even from very early cases, in which the alveoli in some areas of the section did not contain leucocytes and occasionally red cells in small numbers. Leucocytes when present were most abundant in the alveoli opening directly into the terminal bronchioles. The alveolar walls were wrinkled and broadened and definitely infiltrated with mononuclear cells (Fig. 6). This infiltration was most marked in the alveolar walls adjacent to the bronchi but it was present and frequently conspicuous throughout the entire area of atelectasis. Even in non-atelectatic areas of lung there sometimes was some slight to moderate distension of the alveolar walls due to a round cell infiltration. There was a moderate passive congestion of the atelectatic areas as evidenced by dilated and injected pulmonary capillaries. The lymph channels, especially in the interlobular septa, were sometimes dilated and filled with lymph and small numbers of cells. They were not observed to be thrombosed or to contain bacteria. The interlobular septa were frequently widened owing not only to the dilation of the lymph channels but to an apparent pulling apart of the connective tissue elements and to some round cell infiltration. The pleura overlying the atelectatic areas was sometimes wrinkled and thrown into small folds (Fig. 10). It was apparently unaltered otherwise. Lobules lying adjacent to areas of atelectasis were markedly emphysematous, exhibiting extremely thin alveolar walls, many of them broken.

It should perhaps be indicated here that even when all five of the upper lobes of the lung of swine are involved, over half of the actual lung substance remains relatively intact, for the diaphragmatic, or lower lobes, are greater in volume than the five upper lobes. Since it is unusual to have complete atelectasis of all five of the upper lobes, in most cases no more than one-third of the total lung volume is actually involved.

Outside the respiratory tract the histopathology was in accordance with the gross pathological picture. The cervical, mediastinal, and mesenteric lymph nodes were as a rule packed with lymphocytes, the germinal follicles appeared active, and there was much intercellular edema. The histological picture presented by the spleen was that of a slight to moderate, acute splenic tumor characterized by a moderate increase in the mononuclear cells in the pulp and very little, if any, alteration in the Malpighian bodies. The liver was sometimes passively congested but otherwise negative. The kidneys were negative. The mucosa and submucosa of both the stomach and colon showed an increase in mononuclear round cells which was sometimes quite extreme. The blood vessels in these regions were usually dilated and packed with red cells. The goblet cells in the mucosa of the colon were prominent and distended.

As this description shows, the pulmonary pathology differs markedly from that encountered at autopsy in animals succumbing to either the experimental or spontaneous disease.

The Pathology of Fatal Cases.—Death in fatal cases was not necessarily due to pathological changes induced by secondary bacterial invaders, for swine influenza of itself can kill.

The postmortem picture presented by swine dead of the experimentally induced disease was the same as in fatal spontaneous cases. The cervical lymph nodes were much enlarged, edematous, and frequently congested. The mucosa of the trachea and larger bronchi was moderately congested and covered with a thick, tenacious, and sometimes frothy mucous exudate. The smaller bronchi contained a more fluid, blood-tinged exudate and this sometimes in copious amounts. A serosanguineous pleural exudate was frequently encountered. This exudate sometimes contained considerable fibrin and in these cases the anterior lobes of the lung were covered with closely adherent fibrin. Both pleurae were usually involved, although sometimes the process was unilateral. The lungs themselves were voluminous, heavy, and mottled purplish red in color. Palpation revealed that only the apical, azygos, or cardiac lobes were consolidated. That is, the true pneumonia was limited entirely to the portions of lung which in uncomplicated swine influenza would have been atelectatic. The diaphragmatic lobes, which in swine comprise well over half the actual lung substance, exhibited a hemorrhagic type of pulmonary edema which was in most instances extreme. The markings of the interlobular septa were widened by fluid and the lobes as a whole had a glistening swollen appearance. When they were cut across there was an outpouring of a frothy, bloody fluid. There was, as a rule, no fibrin adherent to the diaphragmatic lobes.

Histological examination of sections of the pneumonic areas revealed the pleurae to be usually overlaid with a rich network of fibrin in the meshes of which were myriads of leucocytes. The bronchioles were completely filled with leucocytes, the lining epithelium was badly fragmented and partially desquamated, and the

bronchial walls were densely infiltrated with round cells. The alveoli throughout the section were filled with leucocytes, red blood cells, and coagulated plasma. There was usually no fibrin in the alveolar exudate. The alveolar walls were mildly folded, thickened, and infiltrated, largely with round cells. The lymph sinuses in the interlobular septa were dilated and contained leucocytes, some lymphocytes, and much lymph.

Histological examination of sections of the edematous portions revealed plasma filling the alveoli which also contained small numbers of desquamated epithelial and red cells. There was no fibrin. The cellular exudate in the bronchi was scant but there was much plasma. The bronchial walls were thickened owing to intercellular edema and some round cell infiltration. The pulmonary capillaries were usually dilated and packed with red cells. The lymph sinuses in the interlobular septa and beneath the pleura were widely dilated and contained, in addition to plasma, small accumulations of leucocytes and lymphocytes. The lymph nodes at the hilum of the lung were always enlarged and edematous and usually moderately congested. In some cases, especially those in which a fibrinous pleuritis had been encountered, a serofibrinous pericarditis was also to be observed. The livers of fatal cases of swine influenza were usually engorged and the spleens large, swollen, dark, and friable. An acute diffuse nephritis was occasionally encountered. The stomachs were usually empty except for the presence of moderate to copious amounts of a thin bile-tinged mucus. The small intestines also usually contained considerable bile-tinged mucus. The mucosa of the cecum and the first two-thirds of the colon was intensely hyperemic.

Animals slaughtered during convalescence have much interest from a pathological standpoint. Pulmonary evidence of the disease persisted for 3 or 4 weeks or longer following clinical recovery. Areas of lung were found that were slightly depressed as compared with the adjoining normal tissue. They were grayish pink, on palpation felt firmer than normal, and cut as though fibrous. The bronchi in some instances were dilated and contained a mucopurulent material. Sections revealed much fibrous tissue and great thickening of the alveolar walls.

In animals convalescent from a swine influenzal pneumonia, lung abscess, bronchiectasis, or an obliterative pleuritis were not infrequently encountered at autopsy.

SUMMARY

Swine influenza has been induced in pigs by the intranasal instillation of material from spontaneous cases of the disease as occurring epizootically in eastern Iowa. The experimental disease has the same

features as the epizootic. It has been maintained for study by serial passages accomplished either by intranasal instillation or by pen contact. Eight strains of the virus have been established experimentally during three epizootic periods. The clinical disease induced by these eight strains has been in general the same although its severity and mortality have varied.

The principal features of the pathology of swine influenza are an exudative bronchitis accompanied by marked damage of the bronchial epithelium and its cilia, a peribronchial round cell infiltration, and massive pulmonary atelectasis. The latter is modified somewhat by a round cell infiltration of the alveolar walls. The lymph nodes, especially the cervical and mediastinal ones, are hyperplastic and edematous. There is usually a mild to moderate, acute splenic tumor. The mucosa of the stomach and colon is congested.

The pneumonia following swine influenza is, characteristically, lobular in type and of the same general distribution as the atelectasis. The non-pneumonic areas of lung are extremely edematous and congested.

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EXPLANATION OF PLATES

PLATE 32

FIG. 1. Dorsal aspect of lung in experimental swine influenza (Swine 895) to show the typical appearance and distribution of the massive pulmonary atelectasis. The lymph nodes at the hilum are swollen and edematous. The sharp demarcation between atelectatic and non-atelectatic lung is noteworthy. Animal chloroformed on the 4th day of illness.

FIG. 2. Ventral aspect of same lung.

PLATE 33

FIG. 3. Section of a small bronchus from a normal hog (Swine 588) showing intact ciliated epithelium overlying a normal submucosa. Animal killed by stunning and bleeding. Eosin-methylene blue. × 305.

FIG. 4. Section of a small bronchus from a spontaneous field case of swine influenza (Swine 13) showing fragmented epithelium and extreme round cell infiltration of the submucosa. Animal stunned and bled. Eosin-methylene blue. × 305.

FIG. 5. Section of a small bronchus in experimental swine influenza (Swine 564) 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 5th day following inoculation. Eosin-methylene blue. × 305.

FIG. 6. Section of lung in experimental swine influenza (Swine 473) showing thickening of the alveolar walls in an area of atelectasis. The cells infiltrating the alveolar walls are largely round cells. Animal chloroformed on 3rd day following inoculation. Eosin-methylene blue. × 295.

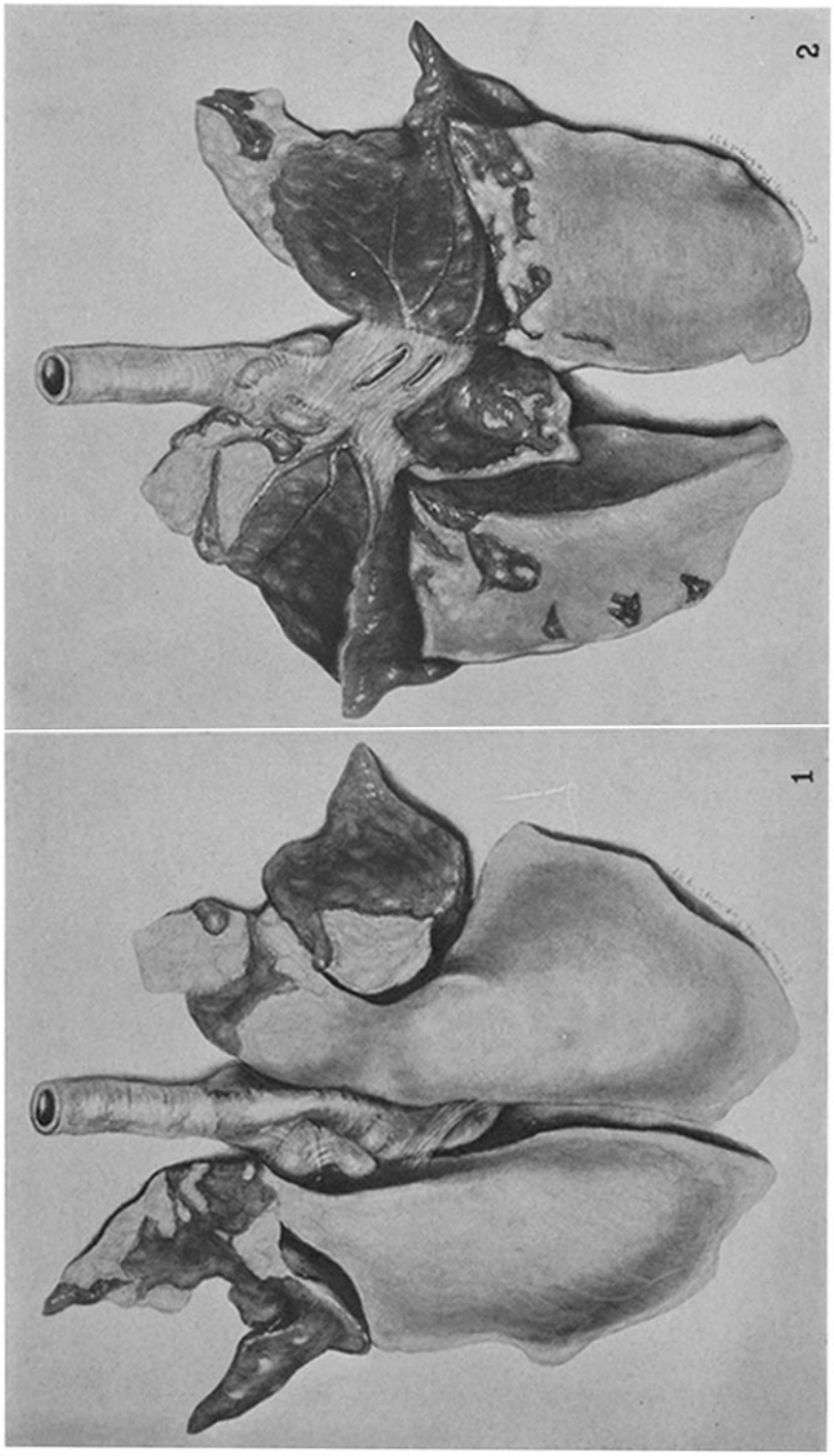
PLATE 34

FIG. 7. Section of lung from a spontaneous field case of swine influenza (Swine 13) showing a bronchus in an area of compensatory emphysema to illustrate better the dense peribronchial round cell infiltration. The lumen of the bronchus contains a dense leucocytic exudate. Animal stunned and bled. Eosin-methylene blue. × 51.

FIG. 8. Section from the lung in experimental swine influenza (Swine 593) showing dense leucocytic exudate in small bronchus and peribronchial infiltration largely with round cells. Animal chloroformed on 6th day following inoculation. Eosin-methylene blue. × 51.

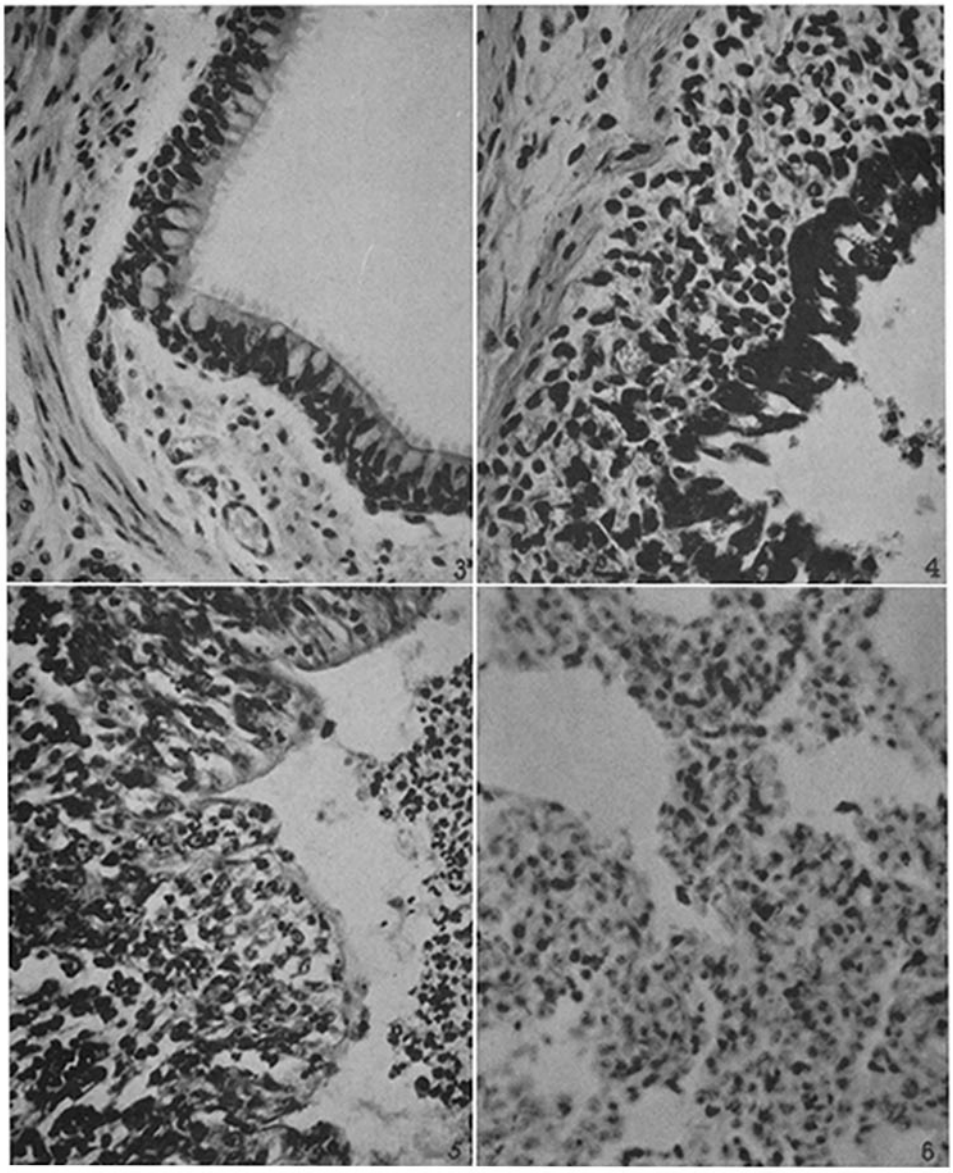
FIG. 9. Section of lung from a spontaneous field case of swine influenza (Swine 97) showing atelectasis with infiltration of the alveolar walls, slight leucocytic exudate in some of the collapsed alveoli, and compensatory emphysema. Animal stunned and bled. Eosin-methylene blue. × 51.

FIG. 10. Section of lung in experimental swine influenza (Swine 454) showing folding of pleura over an area of atelectasis. Animal chloroformed on 3rd day following inoculation. Eosin-methylene blue. × 51.



Painted by Eleanor M. Paxson

(Shope: Swine influenza. I)



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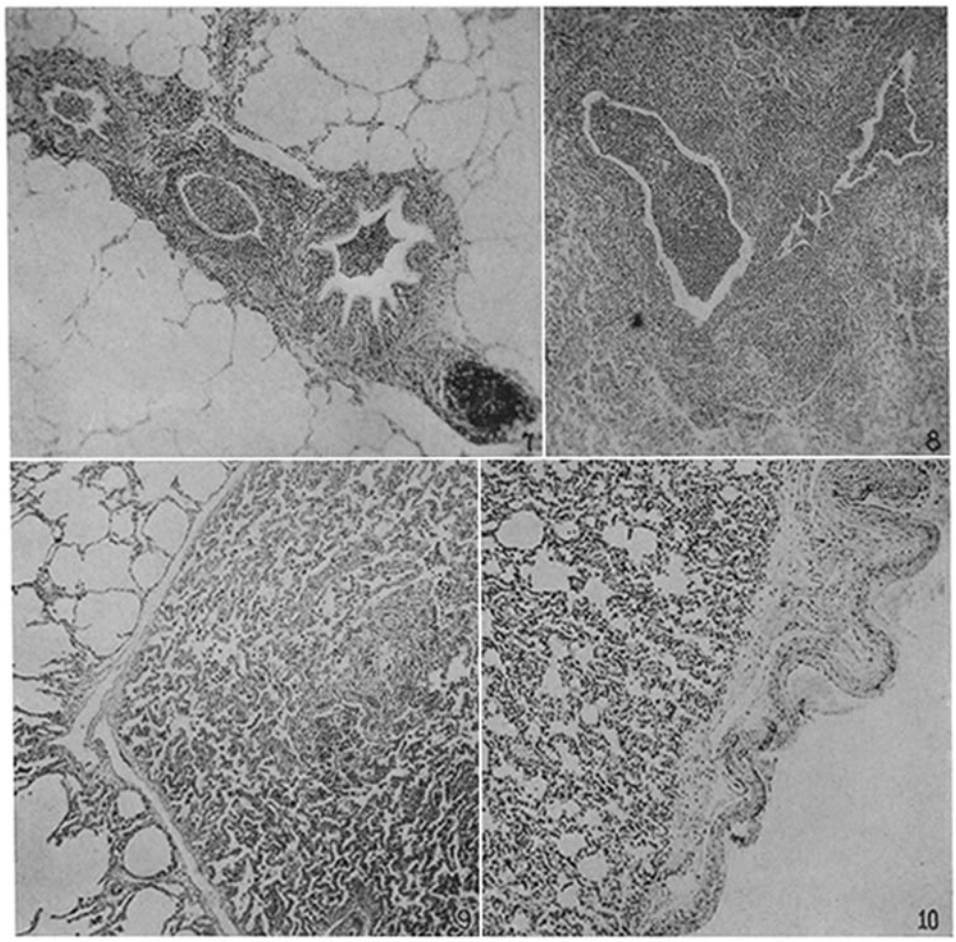

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