STUDIES ON EXPERIMENTAL PNEUMONIA.

X. Pathology of Experimental Influenza and of Bacillus influenzæ Pneumonia in Monkeys.

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Plates 90 to 97.

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The observation has frequently been made that influenza, as it occurs in man, possesses no characteristic pathology. The disease usually manifests itself primarily as a profound intoxication accompanied by a catarrhal inflammation of the upper respiratory tract, which, when uncomplicated, is rarely fatal. So far as known, the inflammatory changes display no properties which differentiate them from those occurring with other types of infection in the same locality. Further confusion is added to the pathology of influenza by reason of the mixed bacteriological findings. While *Bacillus influenzæ* can usually be isolated from the secretions, it is generally found in conjunction with other bacteria, such as streptococcus or pneumococcus. This lack of distinctive features in the pathology of influenza has greatly enhanced the difficulty of identifying the disease in man and of studying it experimentally in animals. None of the earlier investigators made any claims to having transmitted influenza to animals.

Pfeiffer[1] carried out many experiments on various laboratory animals, including monkeys, injecting them intratracheally, intravenously, and directly into the lung tissue, but always without positive results. If large doses of culture were administered the animals usually showed symptoms of toxemia and sometimes died; but he was never able to demonstrate an actual multiplication of the influenza bacilli—a true infection.

In respect to the pathology of *B. influenzæ* pneumonia, accurate knowledge has been almost as difficult to obtain as in influenza. Wollstein and Meltzer[2]

[1] Pfeiffer, R., *Z. Hyg. u. Infectionskrankh.*, 1893, xiii, 357.

[2] Wollstein, M., and Meltzer, S. J., *J. Exp. Med.*, 1912, xvi, 126.

succeeded in producing patches of consolidation in the lungs of dogs by insufflating massive doses of influenza bacilli directly into the bronchi, but with this exception, *B. influenzæ* pneumonia has never been reproduced in animals; and pure *B. influenzæ* pneumonia in man is so rarely encountered that it has been hard to say which of the lesions are due to the influenza bacillus, and which to the other bacteria present. Although *B. influenzæ* pneumonia is usually characterized by the presence of other bacteria, notably the streptococcus and pneumococcus, in addition to the influenza bacillus, pure *B. influenzæ* infections occur, and several investigators have described the pathological picture in such cases (Pfeiffer,[1] MacCallum,[3] and Wolbach[4]).

The descriptions by these writers of the pathology of *B. influenzæ* pneumonia in man are quite similar and indicate clearly that pure *B. influenzæ* infections of the lung produce a characteristic group of lesions. Briefly, these authors describe the condition as follows: Dark red, partially air-containing lungs; slight if any pleural exudate; on section, edema and hemorrhage; purulent bronchitis and bronchiolitis; peribronchial infiltration and thickening; bronchopneumonia; bronchiectasis and emphysema. Microscopically serous and hemorrhagic exudate; dilatation of bronchioles and alveoli; partial destruction of bronchial mucous membrane; pus in bronchi and bronchioles; round cell infiltration and thickening of bronchial walls; infiltration of leucocytes in neighboring alveolar walls; leucocytes and desquamated epithelium in adjacent alveoli; deposit of hyaline material on alveolar walls; organization.

In the preceding article[5] it has been shown that by inoculating monkeys intranasally with a virulent culture of *Bacillus influenzæ*, an infection of the upper respiratory tract may be induced which is clinically comparable to influenza in man, and furthermore, that intratracheal injections of virulent influenza bacilli excite in monkeys a bronchopneumonia analogous to *Bacillus influenzæ* pneumonia in man. In the present paper the pathological findings of experimental *Bacillus influenzæ* respiratory infections will be discussed in detail.

As influenza in man is practically never a fatal disease unless complicated by pneumonia, there has been little or no opportunity for studying the general pathology of the disease. There is no reason to believe, however, that simple influenza is regularly accompanied by

[3] MacCallum, W. G., *J. Am. Med. Assn.*, 1919, lxxii, 720; The pathology of the pneumonia in the United States Army camps during the winter of 1917–18, Monograph of The Rockefeller Institute for Medical Research, No. 10, New York, 1919.

[4] Wolbach, S. B., *Bull. Johns Hopkins Hosp.*, 1919, xxx, 104.

[5] Blake, F. G., and Cecil, R. L., *J. Exp. Med.*, 1920, xxxii, 691.

extensive pathological changes in the various internal organs. It appears to be a local infection of the upper respiratory tract, the general symptoms of such infection probably being referable to absorption of toxic substances. Briefly, it may be said that uncomplicated influenza in man is characterized by swelling and hyperemia of the nasal and pharyngeal mucous membrane with a variable amount of mucoid discharge which later may become profuse and mucopurulent, and usually by acute inflammatory changes in the trachea and larger bronchi. Injection of the conjunctivæ and flushing of the face are also frequently seen. In uncomplicated cases there is little evidence pointing to significant pathological lesions of the internal organs.

Pathology of Experimental Influenza in Monkeys.

In the preceding paper the method of producing experimental influenza in monkeys has been described in detail, and will, therefore, not be repeated here.

In Table I the monkeys that were infected by the inoculation of virulent influenza bacilli into the nose and throat are presented, with the dose injected and the pathological findings in each. Three of these monkeys (Nos. 158, 160, and 161) were not killed. They presented, however, all the clinical signs of acute rhinitis and acute tracheitis. The remaining nine monkeys were killed during, or immediately following their infection, and were subjected at once to complete autopsy.

Rhinitis.—By referring to Table I it will be seen that at autopsy each of the nine monkeys showed acute rhinitis, and that in five out of the nine *Bacillus influenzæ* was recovered by culture or film from some part of the upper respiratory tract (Nos. 148, 139, 153, 157, and 159). The nasal mucous membrane in these nine monkeys presented very much the same appearance. The mucosa was swollen and intensely reddened, especially over the turbinates. The blood vessels were congested, and the mucous membrane was covered with a mucoid or mucopurulent exudate. In short, the process was analogous to acute rhinitis in man.

Microscopic sections from the nasal mucous membrane show an exudate of mucus, pus cells, and desquamated epithelial cells on the

TABLE I.

Monkeys That Received B. influenzæ in the Nose and Throat.

Monkey No.	Date of inoculation.	Amount inoculated.		Date killed.	Pathological findings.	Autopsy cultures.
		Nose.	Throat.			
	1919	*cc.*	*cc.*	*1919*		
150	Aug. 25	2.0	1.0	Aug. 28	Rhinitis; tracheobronchitis; hyperplasia of thymus.	Nasal m. m., Staph. A. Tr., B. I.; Str. V.
140	" 26	Swab.	Swab.	" 29	Rhinitis; tracheobronchitis.	Turb., Staph. A.; large Gr.-neg. bac. Tr., B. I; Staph. A.; Str. V.
148	" 26	"	"	" 28	" hyperplasia of thymus.	Turb., B. I.; Staph. A. Tr., n. g. Lungs, n. g.
142	" 26	0.5		" 29	" sinusitis of left antrum; bronchopneumonia, R. L.	Left antrum, Str. V. Tr., n. g.
139	" 26	0.5		" 28	Rhinitis; bilateral sinusitis; tracheobronchitis; hyperplasia of thymus.	Right antrum, B. I. pure. Left " " " Tr., n. g.
153	" 26	1.0		" 29	Rhinitis; tracheobronchitis; sinusitis of left antrum; hyperplasia of thymus and cervical lymph glands.	Left antrum, n. g.; few B. I. in films. Tr., n. g.; few B. I. in films.
154	" 26	Swab.	Swab.	" 29	Rhinitis; tracheobronchitis; hyperplasia of thymus and cervical lymph glands.	" B. I.; Str. V.; Gr.-neg. micr.

157	Aug. 26	2.0	1.0	Aug. 29	Rhinitis; tracheobronchitis; bilateral sinusitis of antra; hemorrhagic edema of lungs and bronchopneumonia, R. U., L. U., R. L.; hyperplasia of thymus and thoracic lymph glands; bronchiectasis; emphysema.	Left turb., B. I.; Staph. A. Right antrum, B. I.; Gr.-neg. coccus. Tr., n. g. Both br., pure B. I. R. U., pure B. I. R. L., " " L. U., no B. I.; 6 col. Str. V.
158	" 27	2.0	1.0	Not killed.	(Rhinitis; tracheitis.)	
159	" 27	2.0	1.0	Sept. 1	" tracheobronchitis; bilateral sinusitis of antra; hemorrhagic edema of lungs; bronchopneumonia, L. U., L. M., R. U.; organizing pneumonia, L. L.; hyperplasia of thymus and thoracic lymph glands.	Tr., B. I.; few Gr.-neg. micr. and Str. V. Br., B. I.; Gr.-neg. micr. Left antrum, B. I.; Str. V. Right " pure B. I. L. U., pure B. I. L. M., n. g. L. L., pure B. I.
160	" 27	1.5	1.0	Not killed.	(Rhinitis; tracheitis.)	
161	" 27	1.5	1.0	Not killed.	" "	

R. L., L. L., etc., indicate lobes of the lung.

Br. indicates bronchus; m.m., mucous membrane; turb., turbinates; n. g., no growth; Staph. A., *Staphylococcus albus*; B. I., *B. influenzæ*; Str. V., *Streptococcus viridans*; Gr.-neg., Gram-negative. The other abbreviations are self-explanatory.

surface of the epithelium, which is eroded in some places (Fig. 1). The submucosa is engorged, and is infiltrated with polymorphonuclear leucocytes, many of which are also seen between the columnar epithelial cells. Goblet cells are numerous.

Tracheobronchitis.—In seven of the nine animals (Nos. 150, 140, 139, 153, 154, 157, and 159) the inflammation had extended from the nasopharynx down into the trachea and bronchi. Tracheobronchitis can hardly be called a complication in this instance, since it occurs in monkeys, as in man, in a large percentage of cases. In this group the trachea and bronchi were sometimes reddened, but more often the mucous membrane showed only an injection of the blood vessels and a deposit of mucus over the surface. Cultures from the trachea or large bronchi yielded *Bacillus influenzæ* in five out of seven cases (Nos. 140, 150, 154, 157, and 159). Microscopic sections from the trachea show acute inflammatory changes similar to those found in the nasal mucous membrane (Figs. 2 and 3).

Sinusitis.—Five of the nine cases that were autopsied showed, in addition to rhinitis, an infection of one or both of the antra of Highmore (Nos. 142, 139, 153, 157, and 159). *Bacillus influenzæ* infection of the antrum in monkeys is similar to that in man. The mucous membrane is reddened and swollen and the cavity is partially filled with mucopurulent exudate which in one instance was tinged with blood. Cultures from the antra showed influenza bacilli in three cases (Nos. 139, 157, and 159). Of the remaining two, one revealed influenza bacilli in films (Monkey 153) and the other (Monkey 142) yielded *Streptococcus viridans*, probably a secondary invader that had supplanted the influenza bacillus.

Hyperplasia of the Lymph Glands.—The cervical lymph glands were enlarged in two monkeys (Nos. 153 and 154). Microscopic sections show hyperplasia of the follicles, with an increased number of leucocytes in the sinuses.

Hyperplasia of the Thymus.—One of the most interesting changes observed in these monkeys was a well marked hyperplasia of the thymus gland. This condition was entirely unexpected, and so far as known has not been described in *Bacillus influenzæ* infections in man. In seven of the nine monkeys that were autopsied (Monkeys 150, 148, 139, 153, 154, 157, and 159) the thymus gland was definitely

enlarged, in some instances extending down for a considerable distance over the pericardium. The gland was rather firm and had a peculiar pinkish yellow, flesh-like appearance. The lobules were readily recognized. Microscopic sections show marked hyperplasia of the follicles, due to proliferation of the large cells composing the chyme centers. The lymphatic channels leading to the gland are greatly dilated and filled with coagulated plasma. Even the small channels in the center of the follicles are often dilated, and, in addition, contain a considerable number of polymorphonuclear leucocytes and eosinophils. In some instances the interstitial tissue between the lobules is densely infiltrated with leucocytes.

The following case of experimental influenza illustrates the lesions above described and is reported in full.

Protocol 1.—Monkey 139. *Cebus capucinus*, female; weight 1,405 gm. Aug. 26, 1919. Injected with 0.5 cc. of *B. influenzæ* peritoneal exudate intranasally. Aug. 28. Killed by blow on cervical vertebræ.

Autopsy.—Subject is a small brown Capuchin. Thymus shows moderate enlargement. Pericardium and pleura normal; heart is not enlarged; myocardium and valves normal. Trachea and bronchi contain a moderate quantity of mucus. Bronchial lymph glands are not enlarged. Nasal cavities contain a considerable amount of mucopurulent material. Turbinates on both sides are swollen and reddened and their vessels stand out prominently. The right antrum contains 10 or 12 drops of cloudy fluid; the mucous membrane is swollen and edematous. The left antrum also contains cloudy fluid and is similar in appearance to the right. The lungs are pale and voluminous and free from consolidation. Abdominal organs present nothing of importance.

Cultures.—Right antrum, pure culture of *B. influenzæ*; left antrum, pure culture of *B. influenzæ*; trachea, no growth.

Anatomical Diagnosis.—Acute rhinitis; acute bilateral sinusitis; acute tracheobronchitis; hyperplasia of thymus.

Microscopic Examination.—Trachea.—Blood and mucus on surface of epithelium, which shows many goblet cells. Vessels of submucosa engorged; infiltration of leucocytes beneath epithelium. *Turbinate.*—Mucous membrane covered with a thick layer of exudate composed of red blood cells, leucocytes, and desquamated epithelial cells (Fig. 1). The epithelium is eroded in many places. Numerous leucocytes are working their way out between the epithelial cells. There is infiltration of leucocytes in the submucosa. Blood vessels of submucosa are distended with red blood cells. *Lungs.*—Normal. *Thymus.*—Shows hyperplasia of follicles and distention of lymph channels with coagulated plasma.

Three of the monkeys in this group developed bronchopneumonia (Nos. 142, 157, and 159), which is a complication of such importance that it will be discussed in considerable detail.

Pathology of Bacillus influenzæ Pneumonia in Monkeys.

Bacillus influenzæ Pneumonia Developing Spontaneously in Monkeys with Experimental Influenza.

In three of the twelve monkeys inoculated in the nose and throat with *Bacillus influenzæ*, the infection in the upper respiratory tract extended down into the bronchioles with the production of a bronchiolitis, peribronchiolitis, and bronchopneumonia.

Protocol 2.—Monkey 142. *Cebus capucinus*, female; weight 1,300 gm. Aug. 26, 1919. Received 0.5 cc. of *B. influenzæ* peritoneal exudate in the nasal cavities. Aug. 29. Killed.

Anatomical Diagnosis.—Acute rhinitis; acute sinusitis of left antrum; bronchopneumonia, right lower lobe.

Autopsy.—Subject is a small Capuchin; weight 1,300 gm. Lungs show no definite consolidation in the gross. Turbinates greatly swollen and reddened and covered with mucus. Left antrum contains blood-tinged cloudy fluid. Right antrum is clear.

Cultures.—Left antrum, *Streptococcus viridans*; trachea, no growth.

Microscopic Examination.—Turbinates.—Extensive infiltration of leucocytes in mucosa and submucosa. *Right lower lobe.*—Shows an acute bronchiolitis with early pneumonic changes. At certain points the epithelium of the bronchiole is absent and its place taken by a deposit of fibrin and leucocytes. The wall of the bronchiole is infiltrated with polymorphonuclear leucocytes and lymphoid cells and the infiltration extends into the alveolar walls of the adjacent tissue. The capillaries of the alveolar walls are markedly distended in this neighborhood, and a few red blood cells and leucocytes have escaped into the alveoli. The changes, however, are for the most part interstitial and sharply limited to the vicinity of the bronchioles. Section of the right lower lobe stained for bacteria shows no influenza bacilli or other bacteria.

This case illustrates *Bacillus influenzæ* pneumonia in the very earliest stage and indicates that the process is essentially peribronchiolar; in other words, a true bronchopneumonia. Unfortunately, the pneumonia was so early that it was not recognized at autopsy, so no cultures were taken from the lungs. There is every reason to believe, however, that *Bacillus influenzæ* was the exciting agent.

The second case presented a more extensive *Bacillus influenzæ* pneumonia. In this animal the process was readily recognized during life and at autopsy. The lungs showed the hemorrhagic edema and type of consolidation so frequently seen in *Bacillus influenzæ* pneumonia in man.

Protocol 3.—Monkey 157. *Macacus syrichtus*, male; weight 5,200 gm. Aug. 26, 1919. Received 2 cc. of *B. influenzæ* peritoneal exudate intranasally; also received 1 cc. of same peritoneal exudate in the throat. Aug. 29. Killed.

Anatomical Diagnosis.—Acute catarrhal rhinitis following instillation of *B. influenzæ*; bilateral sinusitis of antra of Highmore; acute tracheobronchitis and bronchiolitis; hemorrhagic edema of lungs; bronchopneumonia; vesicular emphysema; bronchiectasis; hyperplasia of thymus and thoracic lymph glands.

Autopsy.—Subject is a large male *Macacus*. Thymus moderately enlarged. A few old adhesions in both pleural cavities. The greater part of the right upper lobe is intensely congested and dark red in color. Emphysematous lobules stand out prominently over the engorged area. A small portion of the upper posterior part of the right lower lobe shows a similar engorgement and emphysema. There is a small patch of engorgement at the root of the right middle lobe. The cut surface of the involved portion of the right lung is dark red and oozes a considerable quantity of bloody fluid. The bronchi are very conspicuous on the cut surface and appear to be much distended. The left upper lobe is covered with old fibrous tags. There is a large area of engorgement along the posterior border similar to that in the right upper lobe. The bronchial lymph glands are greatly swollen. The mucous membrane of the trachea and bronchi is congested and covered with blood-tinged mucus. Liver and kidneys show slight cloudy swelling. Other abdominal organs present nothing of importance. Testes normal. Rectus abdominis muscle appears normal. Nasal mucous membrane is reddened and covered with mucus. Turbinates, especially the left, are intensely swollen and engorged, and have a purplish tinge. Both antra contain pus.

Cultures.—Left turbinate, *B. influenzæ* and *Staphylococcus albus*; right antrum, *B. influenzæ* and Gram-negative coccus; trachea, no growth; both bronchi, pure culture of *B. influenzæ*; right upper lobe, pure culture of *B. influenzæ*; right lower lobe, pure culture of *B. influenzæ*; left upper lobe, six colonies of *Streptococcus viridans*.

Microscopic Examination.—Turbinates.—Marked swelling of the epithelial cells. There is a deposit of blood and mucus on the surface of the epithelium. A considerable number of leucocytes are found working their way between the epithelial cells and there is moderate infiltration of leucocytes in the submucosa. *Trachea.*—Deposit of mucus containing leucocytes on surface of the epithelium. Many goblet cells; a considerable number of polymorphonuclear leucocytes working their way out between the epithelial cells. *Right upper lobe.*—Shows pneumonic process in several phases. In some places there are marked edema and

engorgement (Fig. 4). In other places the alveoli are filled with serum and red blood corpuscles, while at still other points an exudate of leucocytes, fibrin, and desquamated epithelial cells fills the alveoli. The process is very irregular and peribronchiolar in distribution. There is a striking absence of the perivascular edema and infiltration of leucocytes so frequent in pneumococcus and streptococcus pneumonia. Another feature is the marked alveolar emphysema which is seen at many points (Figs. 4 and 5). The alveoli are much larger than normally and the alveolar walls are thin. In many places the great distention of the alveoli has resulted in rupture of the walls. The bronchioles contain blood and coagulated plasma and in some places a leucocytic exudate (Fig. 5). The walls of the bronchioles are infiltrated with leucocytes, and their epithelial lining has been destroyed in places. Some of the bronchi and bronchioles are greatly dilated (Fig. 6), and their epithelial cells show marked flattening. There are chronic inflammatory changes with organization about some of the blood vessels, but these appear to be the sequel of an old infection. There are a few minute intracellular Gram-negative bacilli, all in the leucocytes in the alveoli or bronchioles. *Right lower lobe.*—There is considerable interstitial infiltration of leucocytes in the neighborhood of the bronchioles, and in such areas the alveoli also contain exudate. Emphysema well marked. There are a few influenza bacilli in some of the alveoli. The bacteria are intracellular, having been phagocytosed by the leucocytes composing the alveolar exudate. *Left upper lobe.*—Considerable congestion, but no exudate. No influenza bacilli found. *Thymus gland.*—Well marked hyperplasia of the follicles. There is considerable infiltration of eosinophils, especially around the small central lymph channels. The larger lymphatic channels are greatly dilated, and are filled with coagulated plasma. *Spleen, testes, pancreas, and rectus abdominis muscle.*—Normal.

The third case of *Bacillus influenzæ* pneumonia following experimental influenza also presented characteristic changes.

Protocol 4.—Monkey 159. *Macacus syrichtus,* male; weight 5,430 gm. Aug 27, 1919. Received 1 cc. of blood broth culture of *B. influenzæ* in each nostril, and 1 cc. in the throat. Sept. 1. Killed.

Anatomical Diagnosis.—Acute rhinitis; acute tracheobronchitis; bilateral sinusitis of antra; hemorrhagic bronchopneumonia, left upper and middle lobes, and right upper lobe; lobar pneumonia, stage of resolution and organization, left lower lobe; hyperplasia of thymus and thoracic lymph glands.

Autopsy.—Subject is a large male *Macacus.* Thymus greatly enlarged, extending down to the middle of the pericardium. It is pinkish yellow and measures 3 inches in length. Pericardial sac normal; heart slightly dilated. The lungs are voluminous. The left upper and middle lobes show, extending outward from the hilum, deep red patches of engorgement and edematous consolidation. In these patches emphysematous air sacs are prominent. Cut surface shows irregular patches of consolidation, and exudes a large amount of bloody frothy

fluid. In the upper and posterior portion of the left lower lobe there is an area of moderately firm consolidation about 3 cm. in length. The cut surface of this area is pale yellowish gray, slightly moist, and has a translucent appearance (old organization). It is sharply defined from the unconsolidated portions of the lobe. The right upper lobe shows a few small patches similar to those in the left upper lobe. The remainder of the lungs is crepitant.

Cultures.—Trachea, *B. influenzæ* and a few Gram-negative micrococci and *Streptococcus viridans*; bronchi, *B. influenzæ* and Gram-negative micrococci; left antrum, *B. influenzæ* and *Streptococcus viridans*; right antrum, pure culture of *B. influenzæ*; left upper lobe, pure culture of *B. influenzæ*; left middle lobe, no growth; left lower lobe, pure culture of *B. influenzæ*.

Microscopic Examination.—Left upper lobe.—Extensive consolidation in one part of the section, which is apparently of some duration, as well advanced resolution and organization are present in many places. The exudate is found chiefly in the alveoli, and consists of lymphoid cells and polymorphonuclear leucocytes. Desquamated epithelial cells are also found in considerable numbers in the alveoli. Some of the alveoli contain plugs of organizing fibrin. There is a thick zone of lymphoid cells and connective tissue around the blood vessels. The lesions are those of a resolving lobar pneumonia. The whole lobe, however, is not implicated. Just beyond the consolidated area, the tissue shows engorgement and hemorrhage into the alveoli. A few influenza bacilli are seen in the bronchi. *Left middle lobe.*—Main bronchus filled with blood and leucocytes. In the neighborhood of the large vessels the lung tissue shows intense engorgement and hemorrhage with extravasation of red blood corpuscles into the alveoli and moderate edema. Pleura has been converted into a thick coat of organizing granulation tissue with a deposit of fibrin on the surface (result of a previous infection). Peripheral portion of section is free from consolidation. There are patches of compensatory emphysema in some places. There are large numbers of influenza bacilli in the bronchi, but none in the alveoli. *Left lower lobe.*—Sections show an extensive exudate in practically all the alveoli, resembling that seen in pneumococcus pneumonia. Resolution and organization are in process. Marked perivascular infiltration. Bronchi filled with pus. No bacteria found. *Trachea.*—Deposit of mucus on surface of mucous membrane; mucosa and submucosa infiltrated with leucocytes (Fig. 2). *Tracheal lymph gland.*—Hyperplasia of follicles and infiltration of considerable number of polymorphonuclear leucocytes in the sinuses. Some of the leucocytes are undergoing disintegration and phagocytosis by macrophage cells. *Turbinate.*—Mucosa for the most part intact, but the epithelial cells are swollen and filled with mucus. Heavy deposit of mucus and leucocytes on surface of mucosa. Leucocytes are seen working out between the epithelial cells, and the submucosa is densely infiltrated with polymorphonuclear leucocytes, lymphocytes, and plasma cells. Blood vessels distended with red blood corpuscles. *Thymus.*—Marked hyperplasia of the follicles, and distention of lymph channels which are filled with coagulated plasma. The small capillaries in the follicles are filled with leucocytes.

In Monkey 159 we have a further illustration of *Bacillus influenzæ* pneumonia, in this instance, however, apparently superimposed on an old unresolved pneumonia of the lobar type. Many of the alveoli contain only desquamated epithelial cells or plugs of fibrin, while others are filled with young connective tissue cells. Such areas resemble an organizing pneumococcus pneumonia. On the other hand, extensive areas of hemorrhage and edema occur, and in the latter places the picture is that of a *Bacillus influenzæ* infection.

These cases of *Bacillus influenzæ* pneumonia in monkeys present altogether a fairly complete reproduction of *Bacillus influenzæ* pneumonia as it occurs in man. Complete absence or scarcity of fibrin, hemorrhage and edema, bronchiolitis and peribronchiolar infiltration, discrete or confluent bronchopneumonia, and, finally, emphysema and bronchiectasis, are characteristic lesions which have been demonstrated in both man and monkey. In these three cases the infection originated in the nose and throat and extended down the bronchial tree to the terminal bronchioles, exciting in them a purulent bronchiolitis. Peribronchiolar infiltration with involvement of the adjacent alveoli followed (Fig. 5). The hemorrhage and edema in these animals probably represent a reaction on the part of the lung to absorbed toxic substances; the emphysema is partially compensatory, but for the most part is doubtless caused by the obstructing plugs of pus in the bronchioles.

Bacillus influenzæ Pneumonia in Monkeys Following Intratracheal Injection of Bacillus influenzæ.

Experimental *Bacillus influenzæ* pneumonia was produced by injecting virulent influenza bacilli directly into the trachea, as described in the preceding paper. In Table II the results of these experiments are catalogued. It will be seen that in one of the ten monkeys injected the results were entirely negative (Monkey 135). In two others a tracheobronchitis developed, but the autopsy showed no involvement of the lungs (Nos. 20 and 108). In the remaining seven a *Bacillus influenzæ* pneumonia was definitely established.

Lobes Involved.—The left lower lobe was involved in six cases, and the right lower lobe in six cases. The left upper lobe showed changes

in five of the monkeys, the right upper lobe in only four. All the lobes were affected in two cases (Nos. 124 and 136).

The influenza bacillus was recovered in pure culture from the lungs in two out of the seven cases (Nos. 124 and 138). It was recovered from the trachea or bronchus in three animals (Nos. 124, 136, and 138). It was also cultivated from the trachea in one of the monkeys that failed to develop pneumonia (No. 20). It was isolated from the heart's blood in only one case (No. 138) and that was in the monkey that developed pericarditis in connection with pneumonia.

As will be seen from Table II the lesion in the lungs is described in seven cases as a bronchopneumonia. The solid hepatized lung, so characteristic of pneumococcus infections, was never observed in these animals. The consolidation was distinctly patchy, though the patches were often confluent, especially around the hilum. The hemorrhage and edema frequently seen in *Bacillus influenzæ* pneumonia in man were present, but were usually less intense in the monkey. The picture in some of these cases was doubtless modified to some extent by the comparatively large amount of culture injected into the trachea. This conclusion is supported by the fact that Monkey 155, injected with 4 cc. of killed culture, also developed moderate bronchopneumonic lesions. Apparently the amount of toxic substance present in the culture was capable in itself of setting up a considerable cellular reaction. Monkey 136 received only 1 cc. of peritoneal exudate and developed a markedly hemorrhagic type of pneumonia, similar to that which developed spontaneously in some of the monkeys with experimental influenza.

On removing the sternum in these cases the lungs were invariably found lying free in the pleural cavities. Neither the fibrinous exudate of pneumococcus pneumonia nor the empyema of streptococcus pneumonia was to be seen. On removing the lungs irregular patches of increased resistance could be made out on palpation, most marked around the hilum and along the posterior border where the foci of consolidation usually coalesced to form larger patches. The surface of the lung over these patches was dark red, or even hemorrhagic, and sharply defined from the surrounding pink tissue (Figs. 7 and 8). On section the patches were dark red and rather gelatinous looking. Bloody fluid could be squeezed from the patches of consolidation.

TABLE II.

Monkeys That Received B. influenzæ Intratracheally.

Monkey No.	Date of injection.	Amount injected.	Date killed.	Pathological findings.	Autopsy cultures.
	1919		*1919*		
124	Aug. 11	5 plates (5 cc.).	Aug. 13	Confluent bronchopneumonia, all lobes; tracheobronchitis; hyperplasia of thymus and thoracic lymph glands.	H. B., n. g. R. L., pure B. I. Tr., " " Br., " "
20	" 14	5 (5 ").	" 20	Tracheobronchitis; hyperplasia of thymus and thoracic lymph glands.	H. B., n. g. Tr., pure B. I.
108	" 14	1 plate (1 ").	" 19	Tracheobronchitis; hyperplasia of thymus and thoracic lymph glands; necrosis of peribronchial lymph glands.	H. B., n. g. Tr., "
136	" 14	1 cc. of peritoneal exudate.	" 19	Hemorrhagic bronchopneumonia, all lobes; edema of lungs; tracheobronchitis; bronchiolitis; hyperplasia of thymus, spleen, thoracic and abdominal lymph glands.	H. B., n. g. L. L., " R. L., " Right br., pure B. I.
135	" 14	1 cc. of peritoneal exudate.	Not killed.		
137	" 19	4 plates (4 cc.).	Aug. 21	Confluent bronchopneumonia, R. U., R. L.; tracheobronchitis; hyperplasia of thymus.	H. B., n. g. R. U., " Tr., "

138	Aug. 19	4 plates (4 cc.).	Aug. 21	Confluent bronchopneumonia, R. L., L. U., L. L.; tracheobronchitis; pericarditis; hyperplasia of thymus and spleen.	L. L., pure B. I. Pericard., pure B. I. H. B., pure B. I. Tr., " "
141	" 22	1 plate (1 ").	" 29	Resolving bronchopneumonia, L. U., L. L., R. L.; hyperplasia of thoracic lymph glands; rhinitis; tracheobronchitis.	H. B., n. g. Tr., " Turb., Staph. A.
149	" 23	4 plates (4 ").	" 28	Resolving bronchopneumonia, L. U., L. L., R. U.; hyperplasia of thymus and thoracic lymph glands; bronchiolitis.	H. B., n. g. L. U., " L. L., " Tr., "
152	" 26	1 cc. of peritoneal exudate.	" 27	Bronchopneumonia, R. L., L. L.; tracheobronchitis; hyperplasia of thymus; mediastinitis.	H. B., " R. L., " L. L., " Tr., "
155	" 26	4 plates (4 cc.) of killed *B. influenzæ*.	" 28	Bronchopneumonia, R. L., L. L.; bronchiolitis.	R. L., " Tr., "

H. B., indicates heart's blood.

Areas of compensatory emphysema were frequently observed, especially toward the periphery of the lobe (Fig. 9). The dense new growth of connective tissue, often found in late influenza pneumonia in man, was not present, no doubt for the reason that the monkeys were killed comparatively early in the course of the infection. The trachea and bronchi contained mucopurulent material, in some cases blood-tinged. The tracheal and interbronchial lymph glands were considerably enlarged.

Microscopically, the changes observed were similar to those which have already been described above in connection with spontaneous *Bacillus influenzæ* pneumonia following an attack of experimental influenza. Sections from the lung show disseminated areas of infiltration which are often located about a bronchiole. The lumen of the bronchiole is filled with polymorphonuclear leucocytes and lymphoid cells, and sometimes red blood cells are mixed with the leucocytes (Figs. 10 and 11). The epithelial lining of the bronchioles is partially or perhaps completely destroyed and the underlying tissue is densely infiltrated with leucocytes (Fig. 11). This infiltration extends out into the adjacent interstitial tissue and the contiguous alveolar walls (Fig. 12) which show intense engorgement of the capillaries. The alveoli in this neighborhood do not escape, but contain red blood cells, leucocytes, and desquamated epithelial cells. At times the engorgement of the alveolar walls is so severe that large numbers of red blood cells extravasate into the alveolar lumen. These foci of exudation may coalesce to form larger areas, but the process never reaches the stage of universal consolidation as seen in pneumococcus infections. Vesicular emphysema is present, but is usually not so striking as that in man. The larger bronchi contain pus and the columnar epithelial cells take on the goblet form. Pus cells are found working their way out between the epithelial cells lining the bronchus, and the submucosa is infiltrated with polymorphonuclear leucocytes and lymphoid cells. The pleura shows little if any deposit of fibrin. There is a striking absence of perivascular infiltration of leucocytes and of the lymphatic involvement, which were a prominent feature in pneumococcus and streptococcus pneumonia.

The following case is an excellent example of the findings after experimental *Bacillus influenzæ* pneumonia.

Protocol 5.—Monkey 136. *Cebus capucinus*, male; weight 1,100 gm. Aug. 14, 1919. Received intratracheally 1 cc. of exudate from peritoneum of monkey with *B. influenzæ* peritonitis. Aug. 19. Killed by blow on head.

Anatomical Diagnosis.—Experimental *B. influenzæ* bronchopneumonia; hemorrhagic edema of lungs; acute tracheobronchitis; bronchiolitis; hyperplasia of the thymus gland; hyperplasia of spleen, thoracic, mesenteric, and retroperitoneal lymph glands.

Autopsy.—Performed Aug. 19. On removing the sternum the lungs are found lying free in the pleural cavities, which are free from adhesions and fluid. The pericardial sac is normal. The anterior surface of the pericardium is partially covered by a greatly enlarged thymus gland, which measures about 0.5 cm. in thickness (Fig. 8). The gland is somewhat triangular in shape with the apex of the triangle pointing upward and the base of the triangle lying transversely across the pericardium. Cut surface of the gland is pale pinkish yellow and homogeneous, with definite lobules. Heart not enlarged. Myocardium and valves normal. Right lung is voluminous. Surface of all three lobes is smooth and glistening and everywhere mottled with small bright red hemorrhagic areas lying close together, in some places confluent, in others separated by narrow gray zones which apparently mark the boundaries between the lobules (Figs. 7 and 8). This hemorrhagic condition is also marked at the base and over the anterior surface of the lobes. The lobes have a boggy consistence and contain considerably less air than a normal lung, but the tissue has not the firm resilient consistence offered by a pneumococcus consolidation. Cut surface of right lower lobe shows engorgement and marked hemorrhagic edema. In the upper and middle lobes the congestion is noticed at the root of the lung and gradually fades out toward the periphery. The upper and middle lobes are similar to the lower lobe but show less involvement. The left lung is similar to the right in respect to its surface. The lower lobe shows the same striking hemorrhagic appearance, and the upper and middle lobes are involved to a less extent. Cut surface of the left lung is similar in general to that of the right. Tracheal and interbronchial lymph glands are enlarged and intensely congested. Trachea and bronchi are filled with bloody frothy mucus. Spleen is definitely enlarged. Cut surface is dark red. Liver and kidneys show cloudy swelling. Suprarenals normal. The retroperitoneal and mesenteric lymph glands are considerably enlarged. Pancreas shows no noticeable changes.

Cultures.—Right lower lobe, no growth; left lower lobe, no growth; right bronchus, pure culture of *B. influenzæ*.

Microscopic Examination.—Right upper lobe.—Intense engorgement of all blood vessels and capillaries. In many places the alveolar walls are greatly thickened on account of the distention of capillaries with red blood cells. In lower half of section there is a small patch of consolidation where the alveoli and their walls are infiltrated with many polymorphonuclear leucocytes. In addition to leucocytes the alveoli contain desquamated epithelial cells and red blood corpuscles. The bronchioles contain pus, and the walls of the bronchioles are infiltrated with leucocytes. Section stained for bacteria shows no influenza

bacilli or other bacteria. *Left lower lobe.*—Section shows engorgement, hemorrhage, and, in some places, considerable emphysema (Fig. 9). Considerable number of red blood corpuscles found in the alveoli. Stained section shows no bacteria. No leucocytic exudate in the alveoli in this section. *Left middle lobe (Fig. 10).*—Shows marked engorgement and hemorrhage similar to that in the left lower lobe. *Thymus.*—The follicles are greatly enlarged, due to hyperplasia of the chyme centers and to the greatly increased number of lymphoid cells. Sinuses are distended, being packed with lymphoid cells. The fatty tissue between the follicles is compressed to a thin layer. No polymorphonuclear leucocytes or bacteria are seen. *Trachea.*—Shows no striking changes. The capillaries beneath the epithelium are engorged. The epithelial cells are swollen and filled with mucus. There is a thin layer of mucus on the epithelial surface in which a few red blood corpuscles and lymphocytes are seen. There is no hemorrhage or cellular infiltration in the submucosa. *Tracheal lymph node.*—Greatly enlarged. The vessels and capillaries are intensely engorged. The follicles show hyperplasia. The lymph channels are distended and filled with lymphoid cells and red blood corpuscles. Many of them contain coagulated plasma. In places there is considerable hemorrhage into the follicles. *Kidneys.*—Appear normal, except for moderate capillary engorgement. *Suprarenals.*—Normal. *Spleen.*—There is a very marked lymphoid hyperplasia, the follicles being greatly swollen, very prominent, and densely packed with lymphoid cells. There is slight congestion of the blood vessels and capillaries. The sinuses are filled with lymphoid cells.

Bacillus influenzæ Pericarditis.—One of the monkeys with experimental *Bacillus influenzæ* pneumonia developed an acute pericarditis (No. 138). Cultures from the pericardial fluid gave a pure growth of *Bacillus influenzæ*. The case is of such unusual interest that the autopsy findings will be given in detail.

Protocol 6.—Monkey 138. *Macacus syrichtus*, female; weight 2,915 gm. Aug. 19, 1919. Injected intratracheally with 4 cc. (four chocolate agar plates) of *B. influenzæ*. Aug. 21. Killed by blow on head.

Anatomical Diagnosis.—Experimental bronchopneumonia (*B. influenzæ*), left upper and lower and right lower lobes; acute serofibrinous pericarditis; chronic fibrous pleuritis, right side; acute tracheobronchitis; hyperplasia of thymus and spleen; focal necrosis in thymus; cloudy swelling of viscera.

Autopsy.—Performed Aug. 21. Subject is a medium sized female *Macacus*. On removing the sternum thymus gland is found considerably enlarged. There are a few adhesions in the right pleural cavity. Left pleural cavity normal. On opening the pericardium a moderate quantity of cloudy fluid escapes. Both the visceral and parietal layers of the pericardium are opaque and show marked edema, but there is very little fibrin. Heart moderately enlarged. Myocardium and valves normal. Left lung lies free in the pleural cavity. Anterior portions appear nor-

mal. Posteriorly, however, there are grayish red translucent patches of consolidation. These areas involve a considerable part of the lower lobe. In the upper lobe the process is less extensive. In both cases the changes appear to start at the hilum and spread outward. The right lung is bound to the chest wall by old fibrous adhesions. On section upper and middle lobes are normal. Lower lobe shows a small patch of pneumonia, similar to that found in the left lung. Tracheal and bronchial mucous membrane is congested and covered with mucus. Liver and kidneys show cloudy swelling. Other abdominal organs appear normal.

Cultures.—Left lower lobe, pure culture of *B. influenzæ*; pericardium, pure culture of *B. influenzæ*; heart's blood, pure culture of *B. influenzæ*; trachea, pure culture of *B. influenzæ.*

Microscopic Examination.—Trachea.—Mucus on epithelial surface. Moderate number of lymphoid cells and polymorphonuclear leucocytes in submucosa. Leucocytes also found between epithelial cells. Another section at bifurcation of trachea shows mucus and pus cells on the mucosa and infiltration similar to that in the other section. *Right lower lobe.*—Sections show extensive infiltration of leucocytes in the peribronchial tissue and in the adjacent alveoli. The exudate consists of polymorphonuclear leucocytes, lymphoid cells, and, in addition to these, the affected alveoli contain desquamated epithelium, and a slight amount of fibrin in some places. Bronchi and bronchioles filled with pus. Deposit of fibrin and leucocytes on the pleura. Perivascular infiltration is not observed. Section stained for bacteria shows many minute Gram-negative bacilli (*B. influenzæ*) in the alveolar exudate, mostly intracellular, being in the leucocytes. No influenza bacilli are found in the alveolar walls. Bronchioles are filled with pus, with considerable destruction of epithelium. Another section from right lower lobe shows interstitial pneumonia. *Left lower lobe.*—Shows infiltration similar to that on right side; small plugs of fibrin in some of the alveoli. Another section shows numerous alveoli filled with dense plugs of fibrin, in which is suspended a moderate number of disintegrating leucocytes. A moderate number of intracellular influenza bacilli is found. This lobe shows bronchopneumonia. A few influenza bacilli are found in the alveoli. *Thymus.*—Marked hyperplasia of the follicles and of the chyme centers. The lymph channels are greatly distended and are filled with coagulated plasma. The connective and adipose tissue surrounding the gland is infiltrated at many points with polymorphonuclear leucocytes. There is an area of necrosis of considerable extent at one point in the parenchyma. *Pericardium and heart muscle.*—Serosa of the pericardium is covered with a thick vascular membrane of granulation tissue on the surface of which there is a deposit of fresh fibrin and polymorphonuclear leucocytes. At some points the exudate is necrotic. There is moderate infiltration of leucocytes in the superficial portion of the myocardium. The muscle fibrillæ show cloudy swelling. *Liver.*—Hydropic degeneration about periphery of lobules. *Kidney.*—Shows definite cloudy swelling; glomeruli congested. *Spleen.*—Hyperplasia of follicles.

Other Pathological Changes Found in Association with Experimental Bacillus influenzæ Pneumonia.—Tracheobronchitis was noted in five out of the seven cases. It differed in no way from the tracheobronchitis already described in connection with experimental influenza. Hyperplasia of the thymus was observed in six of the seven cases, and was also present in the two monkeys (Nos. 20 and 108) which developed only tracheobronchitis following the intratracheal injection of influenza bacilli. The microscopic changes were identical with those already described under experimental influenza.

Enlargement of the tracheal and interbronchial lymph glands was usually noted, and in one case (No. 136) the various groups of abdominal lymph glands also shared in this hyperplasia. Monkey 108 showed focal necrosis in the bronchial lymph nodes, and in Monkey 152 there was an acute mediastinitis. There was hyperplasia of the spleen in two instances (Nos. 136 and 138).

Cloudy swelling of the liver was quite common, and similar changes, though usually less marked, were observed in the kidneys, adrenals, and heart muscle. The testicle showed no degenerative changes. No foci of necrosis were found in the rectus muscles.

Bacillus influenzæ Pneumonia in Man.

Microscopic sections from a number of cases of pure *Bacillus influenzæ* pneumonia in man[6] have been studied in connection with experimental *Bacillus influenzæ* pneumonia in monkeys. Photomicrographs from the lungs of two of the cases are shown in Figs. 13 and 14. A number of the lesions described by Wolbach are well displayed in these reproductions.

The first section (Fig. 13) is from a patient who died on the 13th day of the disease. At autopsy the lungs showed confluent bilateral bronchopneumonia and bronchiectasis. Microscopically, as the photograph shows, there are the characteristic changes in the bronchioles described above. The lumen is plugged with an exudate of leucocytes and red blood cells and the lining epithelium has been destroyed in part. The wall of the bronchiole and the adjacent structures are engorged with red blood cells and infiltrated with leucocytes.

[6] These sections were obtained through the kindness of Dr. S. B. Wolbach.

The alveoli contiguous to the bronchiole are filled with coagulated plasma in which are imbedded leucocytes, red blood cells, and desquamated epithelium. Alveoli further distant from the bronchiole contain coagulated plasma but are mostly free from exudate. The alveolar walls are everywhere engorged with red blood cells.

The second patient died of *Bacillus influenzæ* pneumonia on the 9th day of the disease. The autopsy showed confluent bronchopneumonia of both lungs and hemorrhagic myositis of the pectoral and rectus muscles. Microscopic sections of this case (Fig. 14) show severer lesions than those of the previous case. Engorgement, hemorrhage, and edema are present, but in addition there is an extensive emphysema. A moderate grade of leucocytic infiltration is also noted, many of the leucocytes being of the small mononuclear type. The peculiar hyaline membrane of fibrin described by Wolbach is found lining many of the distended alveoli.

The lesions found in these two cases of *Bacillus influenzæ* pneumonia in man are closely simulated by those observed in the lungs of Monkey 157, which, it will be recalled, developed an attack of *Bacillus influenzæ* pneumonia following experimental influenza.

DISCUSSION.

The pathological changes observed in experimental influenza in monkeys differ in no essential respect from those which occur in human influenza. In both instances the disease manifests itself as an acute catarrhal inflammation of the upper respiratory tract, extending usually from the nasal cavities down into the trachea and bronchi. In both diseases the accessory sinuses are often involved and a secondary bronchopneumonia is a frequent complication.

If, however, experimental influenza in monkeys resembles human influenza, the analogy between experimental *Bacillus influenzæ* pneumonia in monkeys and spontaneous *Bacillus influenzæ* pneumonia in man may be said to be still more striking. For in the case of *Bacillus influenzæ* pneumonia in man there are certain characteristics which differentiate it from the pneumonia excited by other bacteria, and render it readily recognizable by the pathologist. The studies of Pfeiffer, and more recently those of MacCallum and Wolbach, have

defined these peculiar lesions very clearly. The intense engorgement, hemorrhage, and edema, the purulent bronchiolitis, the scattered foci of peribronchiolar consolidation, and the ensuing emphysema and bronchiectasis have been emphasized by these writers as anatomical marks which would distinguish the infection from ordinary lobar and lobular pneumonia of pneumococcus and streptococcus origin.

In the foregoing experiments it has been shown that by the injection into monkeys of virulent influenza bacilli, a type of pneumonia can be induced that corresponds in most respects with that which results from *Bacillus influenzæ* infection of the lungs in man. There are the same characteristic changes in and about the bronchioles, the same hemorrhage and edema, the same focal consolidation, and the same tendency toward emphysema and bronchiectasis in the later stages.

Experimental *Bacillus influenzæ* pneumonia in monkeys differs in one respect from the spontaneous disease in man. The process in monkeys appears to be the expression of a milder infection than that in man. The engorgement and edema are usually less marked in monkeys and the leucocytic infiltration is more pronounced. The difference, however, might reasonably have been expected. The human cases occurred during a very severe epidemic in which *Bacillus influenzæ* had presumably acquired exceptional virulence. The strain which was employed for producing the disease experimentally had been cultivated for weeks on artificial media and it was only with considerable difficulty that even a moderate grade of virulence was conferred on it for monkeys. Moreover, in some of the animals the experimental lesions were induced by massive doses of bacteria which might have possessed enough toxicity to excite independently a certain amount of cellular reaction. That massive doses alone are capable of setting up considerable inflammatory reaction is evidenced by Monkey 155, which received 4 cc. of killed influenza bacilli intratracheally and developed a mild bronchopneumonia with some exudation into the alveoli. In this connection it is interesting to note that when *Bacillus influenzæ* pneumonia developed spontaneously in monkeys as a complication of experimental influenza, the pathological changes of *Bacillus influenzæ* pneumonia in man were even more closely simulated than in the animals in which the disease was produced experimentally by direct intratracheal injection of massive

amounts of culture. Monkey 157, for example, developed *Bacillus influenzæ* pneumonia subsequent to the inoculation of *Bacillus influenzæ* in the nose and throat. The autopsy showed in addition to the peribronchial changes, hemorrhage, edema, emphysema, and bronchiectasis. The most characteristic changes were also observed in the lungs of the monkeys that were inoculated intratracheally with small amounts of culture.

The pathogenesis of *Bacillus influenzæ* pneumonia is apparently different from that of pneumococcus and streptococcus pneumonia. In both the experimental and the spontaneous disease the infection seems to travel down the bronchial tree into the bronchioles and subsequently involves the neighboring alveoli by contiguity. In pneumococcus and streptococcus pneumonia the bacteria penetrate the bronchial mucous membrane almost at once and spread rapidly through the perivascular lymph spaces to the alveolar walls in all parts of the lobe. In *Bacillus influenzæ* pneumonia the bacteria are present in large numbers in the bronchioles and to a less extent in the adjacent alveoli. Influenza bacilli, however, are rarely found in any part of the interstitial tissue, and, as MacCallum has pointed out, the lymphatics are noticeably free from involvement in *Bacillus influenzæ* pneumonia. This may explain why the influenza bacillus rarely invades the blood stream. The influenza bacillus lacks the invasive character possessed by the pneumococcus and streptococcus; consequently the lesions produced by the first organism are focal, while those produced by the last two usually involve extensive areas. The influenza bacillus, growing, in a sense, outside the body, injures chiefly contiguous parts, probably by means of toxic substances which it secretes; the pneumococcus and streptococcus, invading the lymphatics, reach all parts of the lung and excite a massive lesion. MacCallum believes that suppurative bronchiolitis, with peribronchial pneumonia, may be caused in some instances by the streptococcus. There is always a possibility, however, that in such cases the influenza bacillus has been the first to infect the lung and has later been supplanted by the streptococcus as a secondary invader. In view of the experiments reported in this paper such an explanation seems fairly plausible. In a number of cases of experimental *Bacillus influenzæ* pneumonia sterile cultures were obtained from the lungs at autopsy,

but there was no question as to the etiology of the pneumonic process. The influenza bacillus had produced its characteristic inflammatory reaction and had then been overcome by the resistance of the animal.

CONCLUSIONS.

1. Virulent influenza bacilli, when injected into the nose and throat of monkeys (*Cebus capucinus* and *Macacus syrichtus*), excite an acute inflammation of the upper respiratory tract, characterized by swelling and hyperemia of the mucous membrane, infiltration of the mucosa and submucosa with leucocytes, desquamation of epithelial cells, and the production of a mucopurulent exudate. The accessory sinuses are often implicated in the infection.

2. Experimental *Bacillus influenzæ* infections of the upper respiratory tract are frequently accompanied or followed by bronchiolitis, peribronchial infiltration, and bronchopneumonia with hemorrhage and edema in the early stage, emphysema and bronchiectasis in the later stages. In general, the process closely resembles uncomplicated *Bacillus influenzæ* pneumonia in man.

3. The injection of virulent influenza bacilli directly into the trachea of monkeys induces in them an experimental bronchiolitis and hemorrhagic bronchopneumonia, similar in all respects to spontaneous *Bacillus influenzæ* pneumonia.

4. In experimental *Bacillus influenzæ* infections of either the upper or lower respiratory tract the influenza bacillus can usually be recovered during the acute stage by culture, either pure or in association with other bacteria.

5. In experimental *Bacillus influenzæ* infections in monkeys characteristic changes occur in the thymus gland—hyperplasia of the follicles, distention of the lymphatic channels, and infiltration of the parenchyma with leucocytes. This enlargement appears to be merely part of a general hyperplasia of the lymphoid structures in the cervical and thoracic regions.

EXPLANATION OF PLATES.

PLATE 90.

FIG. 1. Monkey 139. Experimental influenza. Section of a turbinate showing engorgement of capillaries in the submucosa, and profuse exudate of mucus and pus cells on the surface of the epithelium. × 100.

FIG. 2. Monkey 159. Experimental influenza followed by *B. influenzæ* pneumonia. Section from the trachea showing infiltration of leucocytes in the mucosa and submucosa. Deposit of mucus and leucocytes on the surface. × 400.

PLATE 91.

FIG. 3. Monkey 137. Experimental *B. influenzæ* pneumonia. Section of the trachea showing acute tracheitis. × 400.

FIG. 4. Monkey 157. Experimental influenza followed by *B. influenzæ* pneumonia. Section from the right upper lobe showing hemorrhage, engorgement, and emphysema. The alveoli contain fibrin and many red blood cells, also a few leucocytes and desquamated epithelial cells. × 100.

PLATE 92.

FIG. 5. Monkey 157. Experimental influenza followed by *B. influenzæ* pneumonia. Section from the right upper lobe showing bronchiolitis, peribronchial infiltration of leucocytes, hemorrhage, and edema. *Cf.* with Fig. 13. × 100.

FIG. 6. Monkey 157. Experimental influenza followed by *B. influenzæ* pneumonia. Section through the entire upper right lobe, showing peribronchial pneumonia, bronchiolitis, marked bronchiectasis, and emphysema. × 3.

PLATE 93.

FIG. 7. Monkey 136. Experimental *B. influenzæ* pneumonia. Hemorrhagic and edematous infiltration. This photograph illustrates the patchy character of the consolidation.

FIG. 8. Monkey 136. Anterior view showing hyperplasia of the thymus, which extends down over the greater part of the pericardial sac.

PLATE 94.

FIG. 9. Monkey 136. Experimental *B. influenzæ* pneumonia. Section through the entire left lower lobe showing hemorrhage, engorgement, and edema, with emphysema. × 3.

FIG. 10. Monkey 136. Experimental *B. influenzæ* pneumonia. Left middle lobe. Bronchiolitis, peribronchiolitis, engorgement, and hemorrhage. × 100.

PLATE 95.

FIG. 11. Monkey 124. Experimental *B. influenzæ* pneumonia. Section of the left lower lobe showing purulent bronchiolitis, partial destruction of the wall of a bronchiole, and peribronchiolar pneumonia. × 130.

PLATE 96.

FIG. 12. Monkey 152. Experimental *B. influenzæ* pneumonia. Section from the left lower lobe showing infiltration of leucocytes in the alveoli and septa adjacent to terminal bronchioles. × 100.

FIG. 13. *B. influenzæ* pneumonia in man (Dr. Wolbach's case). Acute bronchiolitis and peribronchiolar infiltration of leucocytes; engorgement and edema. *Cf.* with Fig. 5. × 100.

PLATE 97.

FIG. 14. *B. influenzæ* pneumonia in man (Dr. Wolbach's case). Extensive hemorrhage, engorgement, and edema; hyaline membrane lining alveoli; emphysema. × 130.

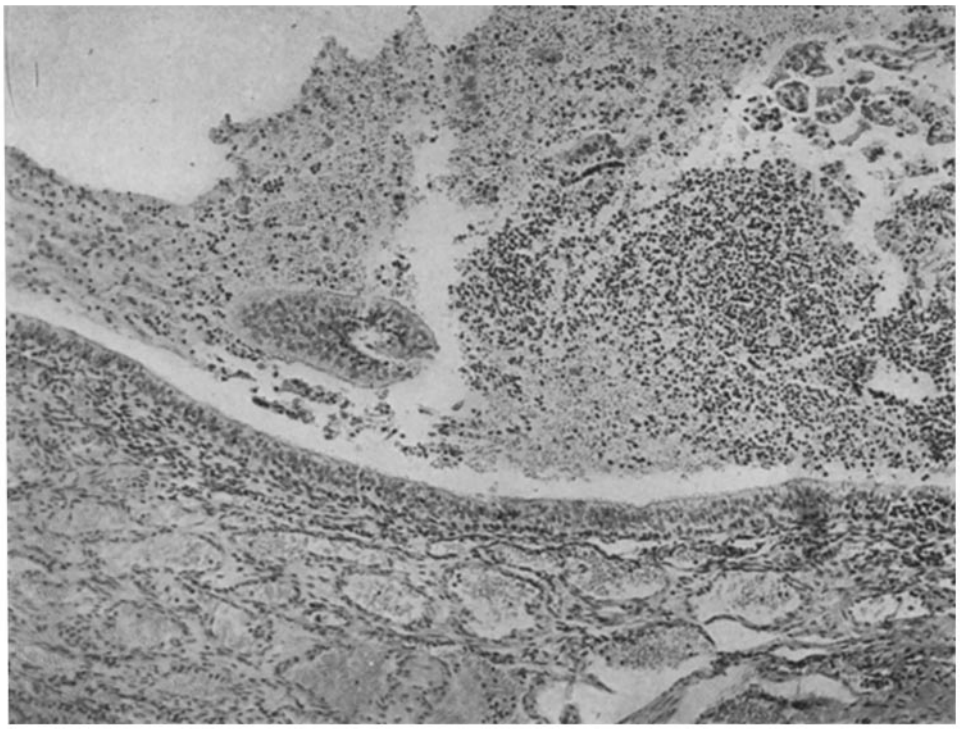


FIG. 1.

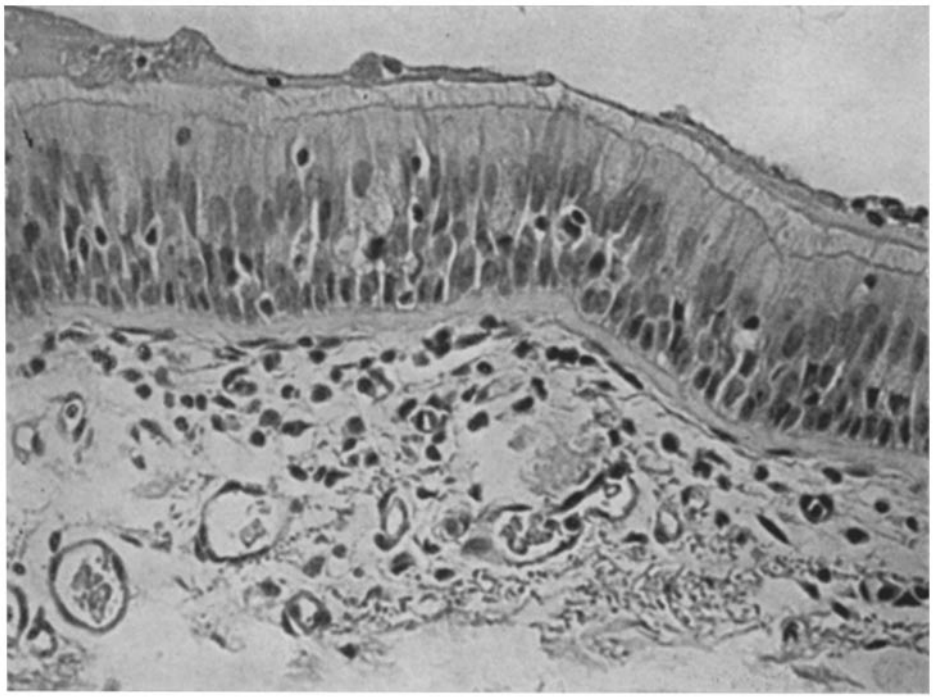


FIG. 2.

(Cecil and Blake: Experimental pneumonia. X.)

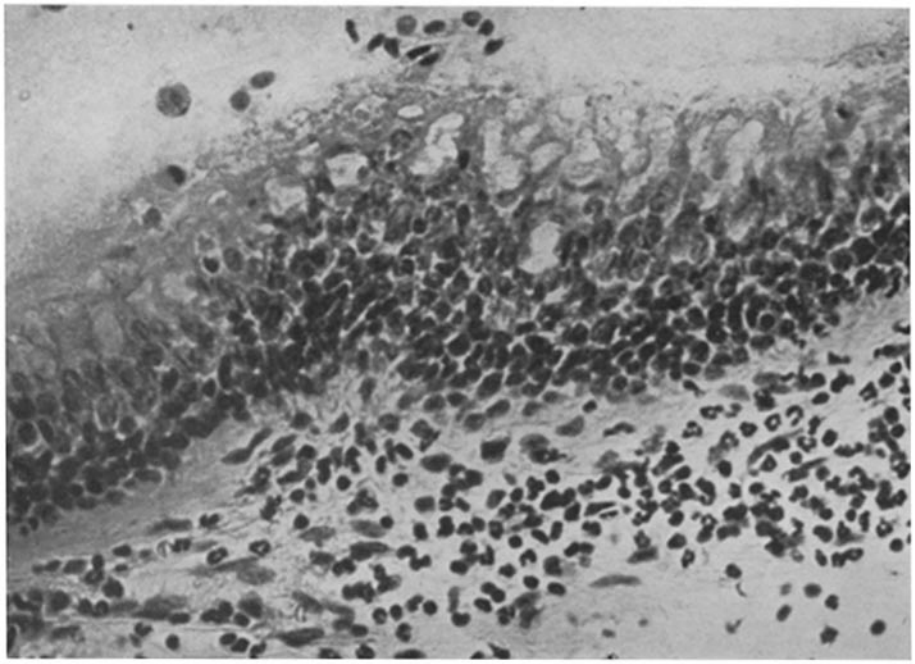
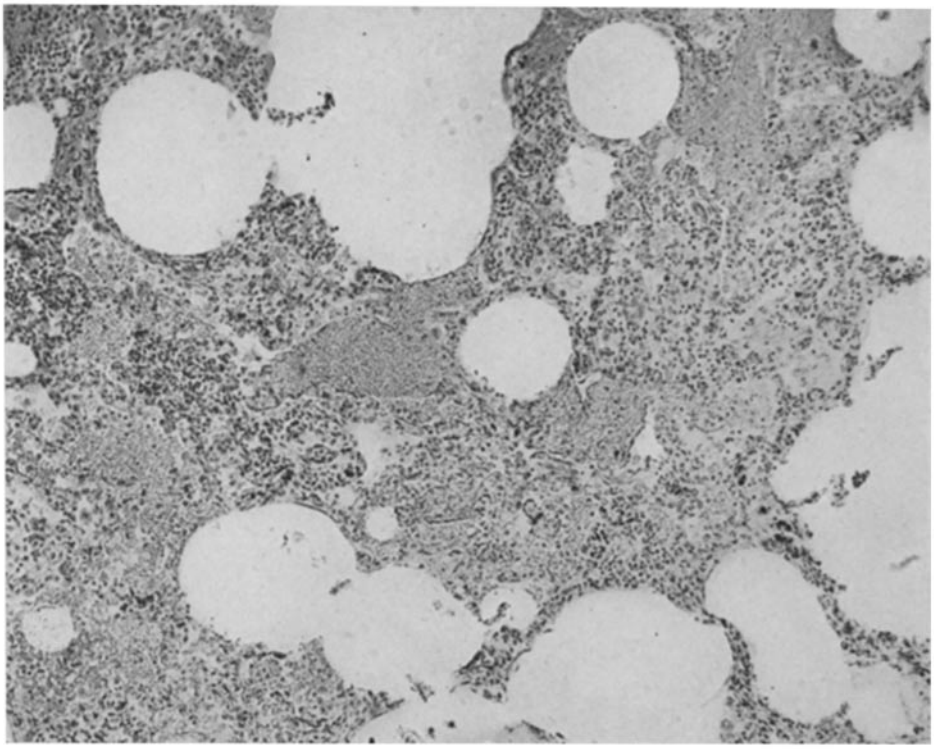


FIG. 3.



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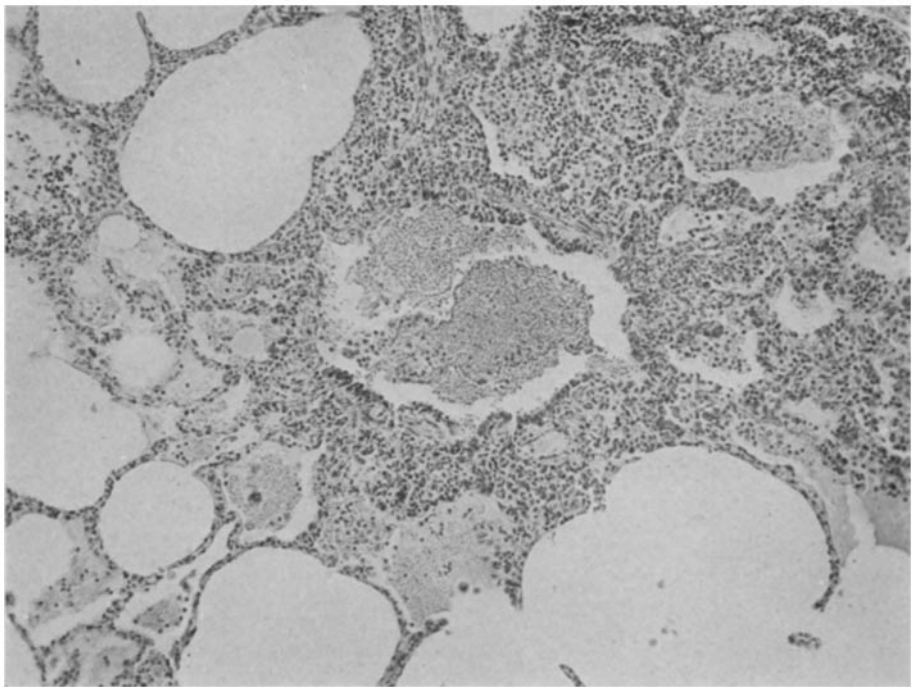

FIG. 5.

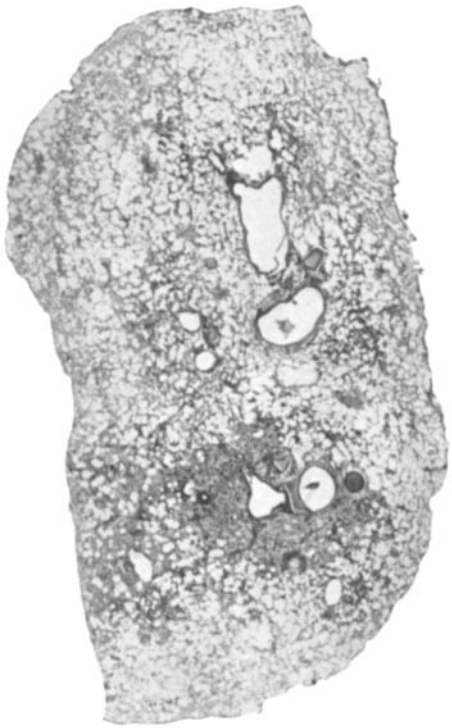

FIG. 6.

(Cecil and Blake: Experimental pneumonia. X.)

FIG. 8.

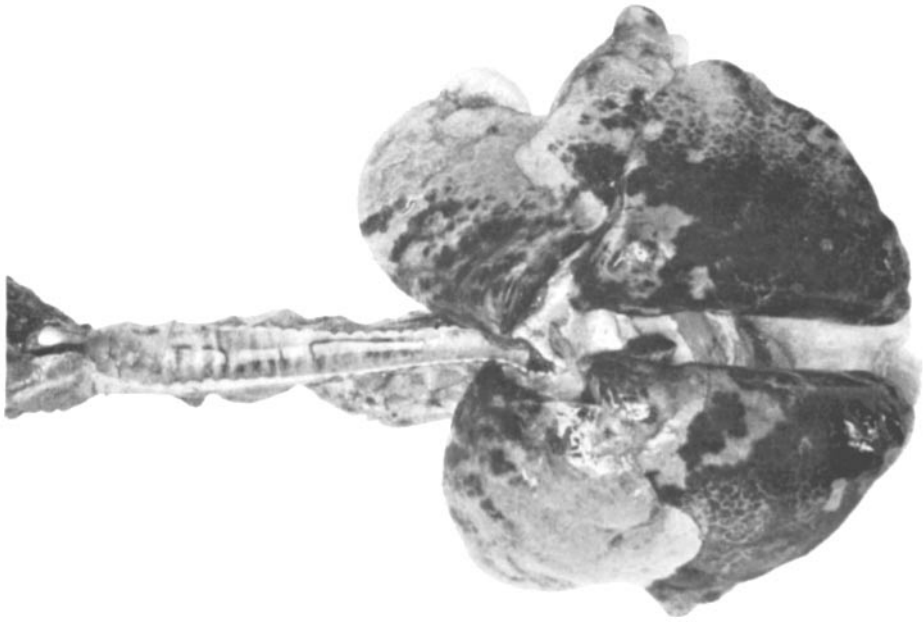

FIG. 7.

(Cecil and Blake: Experimental pneumonia. X.)

FIG. 9.

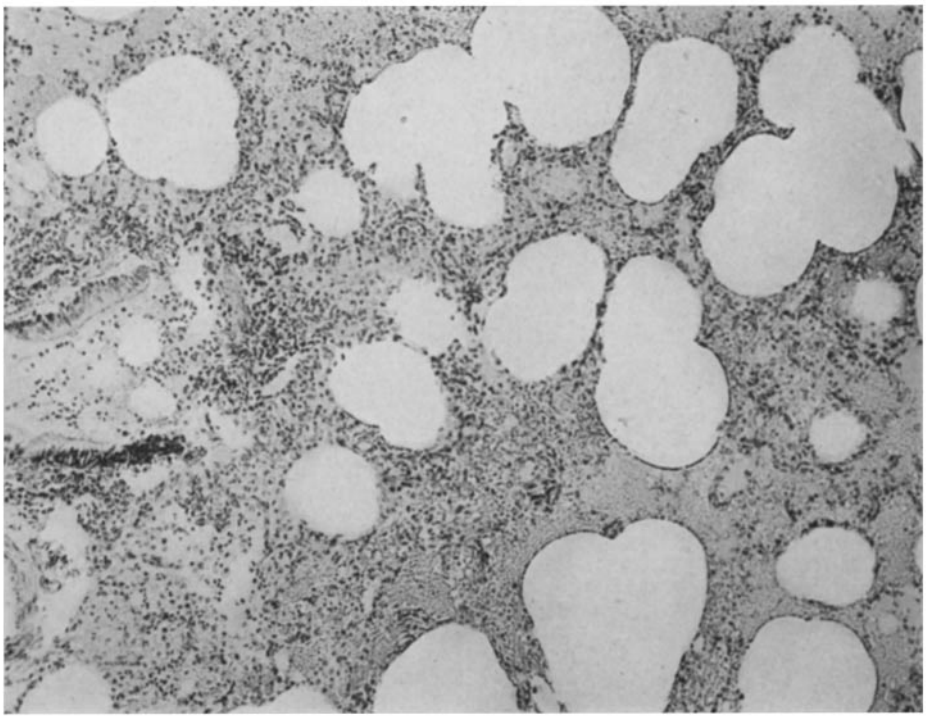

FIG. 10.

(Cecil and Blake: Experimental pneumonia. X.)

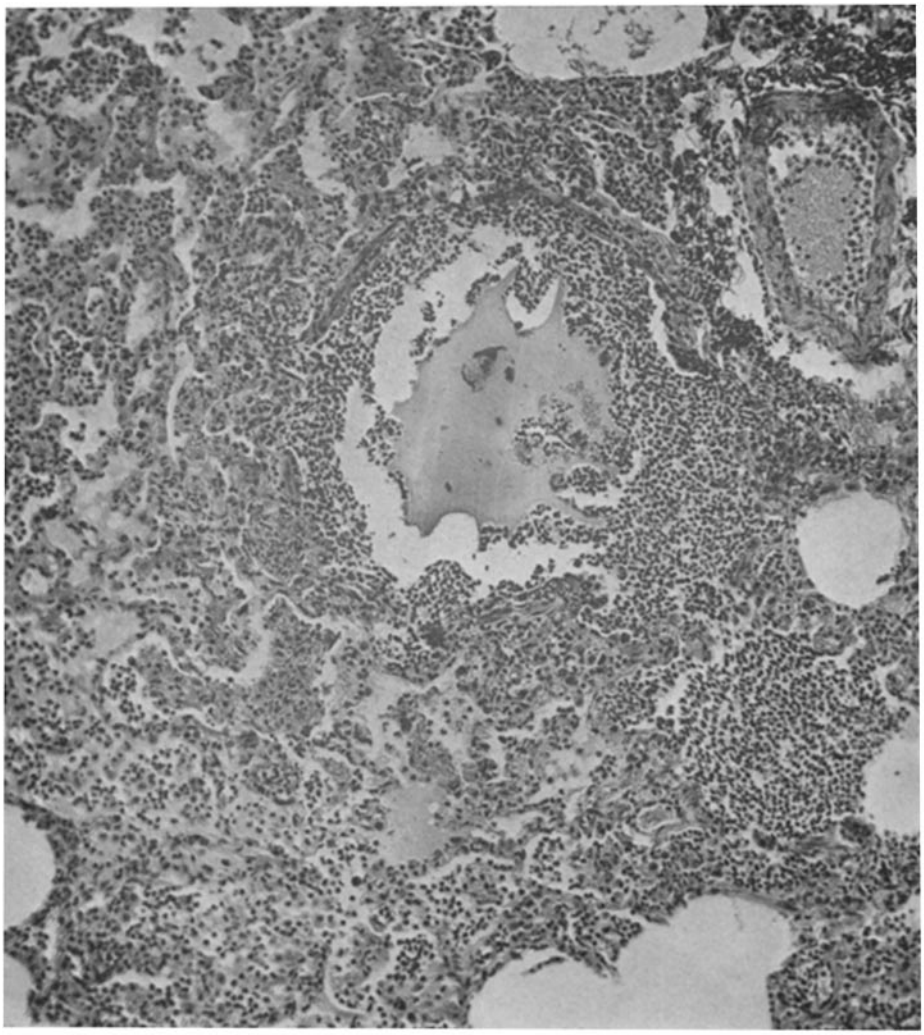

FIG. 11.

(Cecil and Blake: Experimental pneumonia. X.)

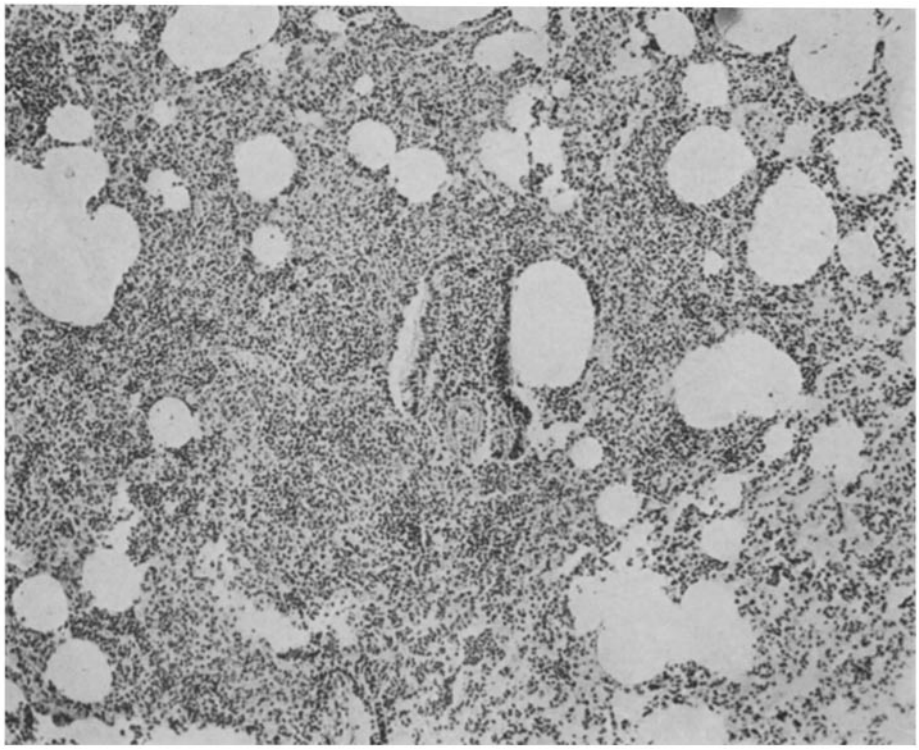

FIG. 12.

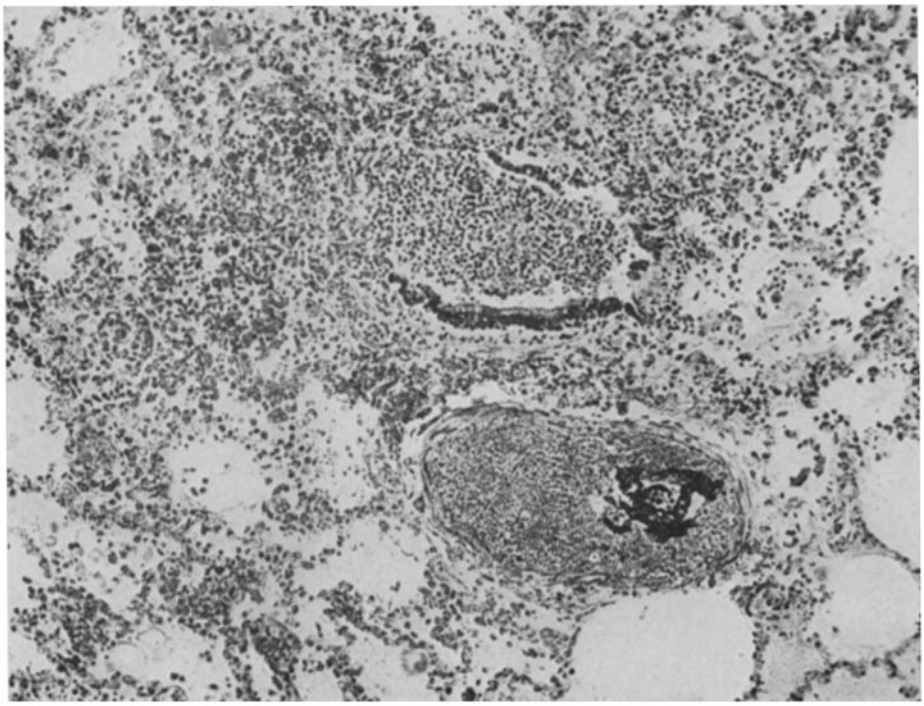

FIG. 13.

(Cecil and Blake: Experimental pneumonia. X.)

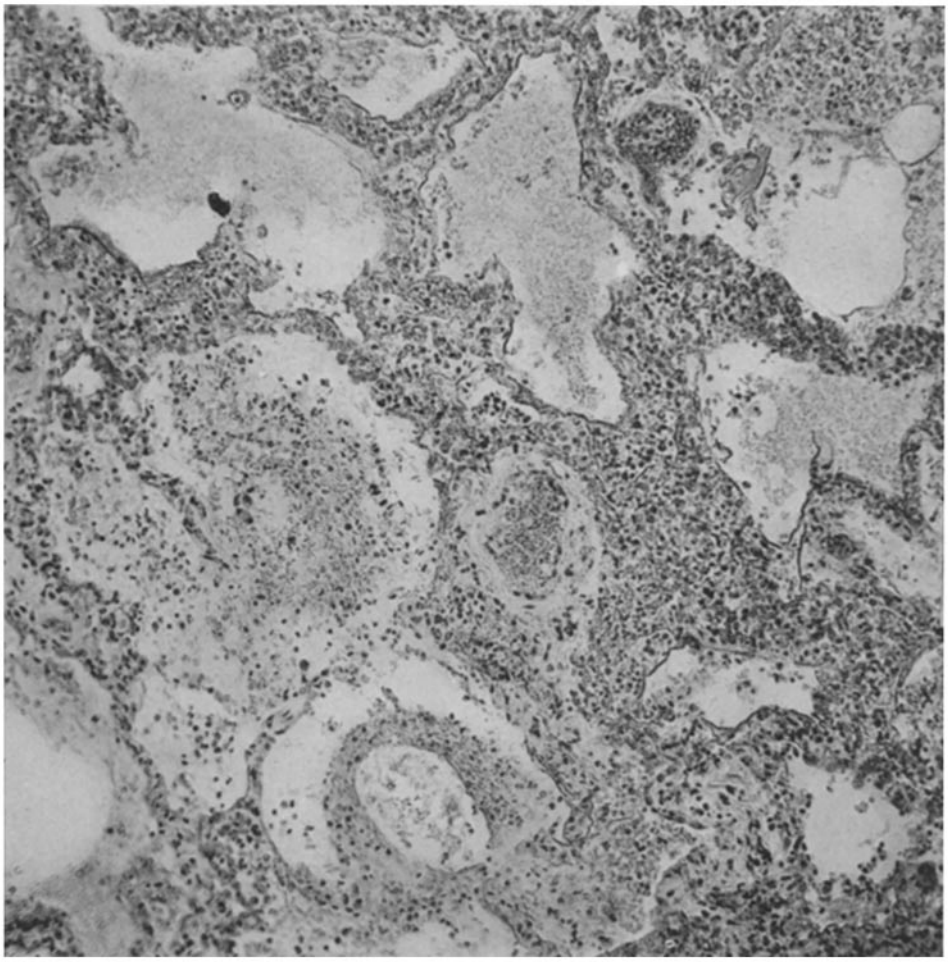

FIG. 14.

(Cecil and Blake: Experimental pneumonia. X.)