STUDIES ON EXPERIMENTAL PNEUMONIA.

II. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys.

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Plates 22 to 44.

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In a preceding paper[1] it has been shown that pneumonia may be produced readily in normal monkeys by the intratracheal injection of minute amounts of pneumococcus culture and that the disease so produced runs a clinical course identical with that of lobar pneumonia in man. In this paper it is proposed, first, to describe the pathology of pneumococcus pneumonia experimentally produced in monkeys, in order to show that the disease is identical with lobar pneumonia in man, and, second, to present observations concerning the pathogenesis of lobar pneumonia based upon study of the pathology of lobar pneumonia in monkeys.

Pathology of Pneumococcus Pneumonia in Monkeys.

Autopsies were performed in 40 cases of pneumonia experimentally produced in monkeys by the intratracheal injection of pneumococcus. Of these, twenty-seven died during the active stage of the disease or later from complications, and thirteen were killed, one on the 9th day of the disease and twelve at varying intervals after recovery by crisis. The cases are summarized in Table I, the fatal cases, including Monkey 26, being arranged according to the duration of the disease, the recovered cases according to the time elapsing between recovery and the killing of the animal for pathological examination. The day of intratracheal injection is considered the 1st day of the disease, since onset of pneumonia had usually occurred within 24 hours after inoculation.

[1] Blake, F. G., and Cecil, R. L., *J. Exp. Med.*, 1920, xxxi, 403.

Macroscopic Pathology.

Macroscopically the lungs at autopsy presented the characteristic picture of lobar pneumonia (Figs. 1 to 3), showing the stages of engorgement, red hepatization, gray hepatization, and resolution. The stage of pneumonia found at autopsy depended primarily upon the duration of the disease at the time of death. This was modified to a certain extent, however, by the amount of pneumococcus culture injected, monkeys receiving a comparatively large amount showing a more advanced involvement early in the disease than those receiving the smaller amounts.

It will be seen from Table I that the lungs of monkeys dying within 5 days after intratracheal injection presented the macroscopic picture of engorgement or red hepatization, and that gray hepatization appeared only subsequently to this. In reality, of course, no such sharp distinction could be made between the different stages of the disease, since, as is well recognized,[2] lobar pneumonia is a progressive process and one stage merges gradually into the next. This was readily observed on examination of the cut surfaces of the lungs and is well illustrated in Fig. 2 in which the right lower lobe shows both red and gray hepatization.

Of the monkeys killed at varying intervals after recovery, five showed an actively resolving pneumonia, two resolution combined with partial organization, and one extensive organization. Organizing pneumonia was also found in two fatal cases (Monkeys 14 and 42) which died at a considerable interval after apparent recovery from the active stage of the disease. The involved lobes in these cases presented a characteristic translucent, grayish appearance, being of a doughy consistency when resolution was occurring, firm and rubbery when organization was taking place.

In three cases of mild pneumonia (Monkeys 82, 96, and 107), in two of which the disease presented the clinical picture of an abortive attack, the lungs showed an interstitial involvement with little or no exudate in the alveoli. In the remaining case (Monkey 75) the pathological picture was complicated by an extensive pulmonary tuberculosis.

[2] Delafield, F., and Prudden, T. M., A text-book of pathology, New York, 10th edition, 1914, 606.

Tabulation of the lobes involved (Table II) shows that in both the fatal and recovered cases the right and left sides were about equally affected and that the lower lobes were about twice as frequently involved as the middle or upper lobes. The extent of the involvement, however, was in striking contrast in the two groups. Of the twenty-eight fatal cases (including Monkey 26) seventeen showed bilateral pneumonia, while of the twelve recovered cases only three showed involvement on both sides. Eighteen of the fatal cases showed pneumonia of three or more lobes, while none of the recovered cases showed involvement of more than two lobes, and in more than half the pneumonia was confined to one lobe.

The distribution and extent of the pneumonic lesions within the lobe in the different stages of the disease has also been studied. In the earliest stages of engorgement before hepatization had begun the most striking feature was a thickening of the vascular adventitia and walls of the bronchi near the root of the lobe (Figs. 4 to 6). This process spread rapidly throughout the lobe, following the ramifications of the vascular and bronchial trees and appeared always to precede exudation into the alveoli. The interlobular septa were similarly, though less conspicuously, involved. Microscopic examination showed that it was due to edema and leucocytic infiltration of the interstitial tissue. It was accompanied by intense capillary engorgement.

By the time this process had extended throughout the lobe hepatization usually had begun. In monkeys that died early in the stage of red hepatization the consolidation was found invariably to occupy the portions of the lobe proximal to the hilum (Figs. 7 and 8). Surrounding the consolidated areas was a zone of edematous alveoli. In the distal portions of the lobe engorgement was found, the alveoli being still air-containing.

With the further progress of the disease the distal portions of the lobe became progressively consolidated until complete lobar hepatization resulted. By the time red hepatization of the distal portions of the lobe had occurred the portions proximal to the hilum and adjacent to the larger bronchi and vessels were found to have assumed the appearance of gray hepatization (Fig. 2). Finally, in monkeys which died after the 6th day of the disease complete lobar

TABLE I.

Autopsy Findings in Experimental Pneumococcus Lobar Pneumonia in Monkeys.

Monkey No.	Date of inoculation.	Type of pneumococcus.	Amount injected.	Day of disease on which death occurred.	Bacteriology.			Lobes involved and stage of disease.						Complications.
					Heart's blood.	Lungs.	Miscellaneous.	L. U.*	L. M.	L. L.	R. U.	R. M.	R. L.	
	1919		*cc.*											
2	Feb. 24	I	0.5	1st	Pn. I	R. L., Pn. I.	Br., Pn. I.	R. H.		R. H.	R. H.		R.H.	
5	Mar. 5	I	0.01	1st	"	R. U., "	" "			E.	E.		"	
1	Feb. 17	I	1.0	2nd	"	R. L., "							"	
3	" 24	I	0.1	2nd	"	L. U., "		R. H.		E.				
29	Apr. 2	I	1.0	2nd	"		Br., Pn. I.	E.	E.	R. H.				
109	May 27	I	0.001	3rd	"	R. M., Pn. I.	" "	"	"		E.	E.		
6	Mar. 5	I	0.001	4th	"	R. L., "	Tr., "				"		R. H.	
17	" 26	I	1.0	4th	"	" "	Pericard., Pn. I.	E.	E.	E.	"	E.	E.	Ac. fib. pericard.
88	May 20	I	0.000001	4th	"	L. L., "	Br., Pn. I.	"	"	"			"	
98	" 20	I	0.000001	4th	"	" "	" "	"		"	E.		"	
23	Mar. 18	I	1.0	5th	"	" "				R. H.			"	
87	May 6	I	0.1	5th	"	" "	Br., Pn. I.	R. H.	R. H.	"			E.(C.).	
101	June 20	I	0.000001	5th	"	" "	" "	E.	E.	E.			E.	
114	" 20	I	0.000001	5th	"	R. L., " L. L., "	" "			"			"	
					S. H.	S. H.	S. H.							
85	May 6	I	0.001	6th	Pn. I	L. L., Pn. I.	Perit., Pn. I.		R. H.	"				Ac. fib. perit.
112	June 5	I	0.01	6th	"	R. L., "				"		R. H.	R. H.	
												G. H.	G. H.	
110	May 27	I	0.000001	7th	"	" "	Br., Pn. I. Pericard., Pn. I.				R. H.	"	"	Ac. fib.-pur. pericard.
83	Apr. 30	I	0.001	8th	"	" "	Pl., Pn. I.				E.	"	R. H.	Serofib.
											R. H.		G. H.	pleurisy.

26	Mar. 21	I	1.0	9th (K.)	N. G.	L. L., N. G. R. L., "	Br., Pn. I.			G. H.			G. H.	
31	Apr. 2	I	0.01	10th	Pn. I	L. L., "	Emp., " Br., "	G. H.	G. H.	"				Emp.; mediast.
100	June 20	I	0.000001	10th	"	" "		R. H.	"	"			E.	
67	May 6	I	0.001	11th	"	R. L., Pn. I.	Br., Pn. I.						G. H.	
30	Apr. 2	I	0.1	12th	N. G.	" N. G. L. L., "		G. H.	G. H.	G. H. Res.	G. H.	G. H.	" Res.	Hyp. and dil. of heart.
80	May 13	I	0.000001	12th	Pn. I	" Pn. I.	Pericard., Pn. I. Br., Pn. I.		"	G. H.			G. H. (C.).	Ac. fib.-pur. pericard.
93	" 15	I	0.001	13th	"	R. L., "	" "				G. H.	G. H.	G. H.	Hyp. and dil. of heart.
86	" 6	I	0.000001	14th	N. G.	L. L., "	" "			G. H.			"	
14	Mar. 26	I	1.0	17th	Pn. I	R. L., N. G.	" N. G.						Org.	
42	Apr. 10	I	0.001	37th	"	L. L., Pn. I.	" Pn. I.		Org.	Org.	Res.	Res.	Res. Org.	
25	" 4	II	0.1	C. 7th K. 7th	N. G.	R. U., N. G.	" N. G.				"			
95	May 13	I	0.00001	C. 11th R. 15th C. 21st K. 23rd	"	L. L., "				Res. Org.				

* L. U., L. M., L. L., etc., indicate lobes of the lung. The cardiac lobe is included as part of the right lower lobe. (C.) indicates pneumonia of the cardiac lobe without involvement of the right lower lobe. Pn. I indicates Pneumococcus Type I; S. H., *Streptococcus hæmolyticus*. Br. indicates bronchus; Tr., trachea; Pl., pleura; N. G., no growth in cultures. E., R. H., G. H., Res., and Org. indicate engorgement, red hepatization, gray hepatization, resolution, and organization, respectively. The stage of pneumonia recorded shows the predominant type of lesion in the lobe as judged by macroscopic examination. K. indicates killed; C., crisis; R., relapse; L., lysis. The other abbreviations are self-explanatory.

TABLE I—*Concluded.*

Monkey No.	Date of inoculation.	Type of pneumococcus.	Amount injected.	Day of disease on which death occurred.	Bacteriology.			Lobes involved and stage of disease.						Complications.
					Heart's blood.	Lungs.	Miscellaneous.	L. U.*	L. M.	L. L.	R. U.	R. M.	R. L.	
	1919		*cc.*											
82	Apr. 30	III	0.1	C. 7th†	N. G.		Tr., N. G.				Res.			
				K. 8th										
107	July 1	III	1.0	L. 4th‡	"	R. L., N. G.	Br., "						Res.	
				K. 5th										
96	" 1	III	1.0	L. 3rd‡	"	L. U., "	" "	Res.			Res.			
				K. 5th										
64	May 6	I	0.000001	L. 27th	"	L. L., Pn. I.	" Pn. I.			Org.				
				K. 30th										
65	" 6	I	0.1	C. 8th	"	R. L., N. G.							Res.	
				K. 12th										
89	" 20	I	0.001	C. 12th	"	" "							"	
				K. 16th										
7	" 27	IV	0.1	C. 8th	"	" "	Br., N. G.			Res.			"	
				K. 13th										
78	" 15	I	0.001	C. 9th	"	" "	" "		Res.				"	
				K. 15th									Org.	
81	" 13	I	0.0001	C. 10th	"	" "	" "					Res.	Res.	
				K. 17th										
75	June 24	II	0.1	C. 8th	"				Res.	Res.				Pulmon. tuberc.
				K. 22nd										

† Interstitial and lobular pneumonia.
‡ Interstitial pneumonia.

consolidation in the stage of gray hepatization was encountered (Figs. 3 and 9).

Pleurisy.—Acute fibrinous pleuritis was almost universally found at autopsy. The fibrinous exudate varied considerably in thickness, depending upon the duration of the disease, and was spread in an easily detachable layer over the surfaces of the involved lobes. In seven cases that died very early there was no evident exudate on the

TABLE II.

Extent and Distribution of Pneumonia in Fatal and Recovered Cases of Experimental Lobar Pneumonia in Monkeys.

	Fatal cases (including Monkey 26).	Recovered cases.
No. of cases	28	12
Left lung involved	21	6
Right " "	24	9
Bilateral involvement	17	3
One lobe involved	3	7
Two lobes "	7	5
Three or more lobes involved	18	0
Left upper lobe involved	12	1
Right " " "	11 (23)	3 (4)
Left middle " "	12	2
Right " " "	8 (20)	1 (3)
Left lower " "	20	4
Right " and cardiac lobes involved	23 (43)	6 (10)

pleura, but microscopic examination showed an early pleurisy. In cases killed after recovery the exudate was undergoing organization.

Complications.—Pneumococcus complications occurred in six cases. Monkey 31 had empyema, Monkey 83 serofibrinous pleurisy, Monkey 17 acute fibrinous pericarditis, Monkeys 80 and 110 acute fibrinopurulent pericarditis, and Monkey 85 localized subdiaphragmatic fibrinous peritonitis. Pneumococci were isolated in pure culture from these complications, which were similar in all respects to like complications of lobar pneumonia in man.

Other Lesions.—Of extrapulmonary lesions the most striking were in the lymph nodes about the hilum and in the bone marrow. The

lymph nodes were consistently enlarged and succulent. Microscopic examination showed that this enlargement was due to distention of the lymph sinuses with numerous large mononuclear cells and lymphocytes, and with moderate numbers of polymorphonuclear leucocytes (Fig. 33). In many instances the large mononuclear cells showed active phagocytosis of polymorphonuclear leucocytes. This process would appear to represent an accumulation of cells brought to the lymph nodes about the hilum by the lymphatic drainage of the lung. Sections of bone marrow taken from the femur showed the widest variation in hematopoietic activity. In some instances the picture was one of almost complete exhaustion, the marrow being entirely devoid of polymorphonuclear leucocytes and largely so of myelocytes (Fig. 34). In others there was marked hyperplasia with greatly increased numbers of leucocytes and myelocytes in the marrow (Fig. 35). All grades of variation between these two extremes were encountered. The picture found depended upon the course of the disease and the degree of infection at the time of death. In monkeys which died during the active stage of the disease with overwhelming pneumococcus septicemia and terminal leucopenia myeloid exhaustion was found. In monkeys which died later without an early overwhelming septicemia but usually with some complication, the picture was one of myeloid hyperplasia. This finding was in keeping with the secondary rise in the leucocyte count exhibited in these cases.

In two animals (Monkeys 30 and 93) marked dilatation and hypertrophy of the heart were found. Both ran a prolonged severe course. Monkey 30 was of particular interest because death occurred suddenly 4 days after apparent recovery by crisis. Autopsy showed nearly complete consolidation of all lobes, cultures from the lungs and heart's blood being sterile. In several other cases running a prolonged severe course, moderate dilatation of the right heart was found, but hardly sufficient to be of certain significance.

Lesions of the abdominal viscera except for cloudy swelling of the liver and kidneys and congestion of the spleen were not encountered.

Microscopic Pathology.

Microscopically, the pneumonia produced in monkeys by the intratracheal injection of pneumococcus likewise showed the characteristic picture of lobar pneumonia in the stages of engorgement, red hepatization, gray hepatization, and resolution or organization. The progressive nature of the process was well shown in monkeys which died at a moderately advanced stage of the disease, in which the microscopic picture of gray hepatization was found in the alveolar tissue proximal to the hilum, of red hepatization in the surrounding zone of tissue, and of engorgement and edema in the more distal portions of the lobe, the peripheral alveoli at the margins most distant from the hilum often being still air-containing.

Engorgement.—As stated above the most striking feature of the stage of engorgement was the perivascular edema and leucocytic infiltration. The walls of the bronchi and the interlobular septa were similarly involved, and extension of the process to the pleura had occurred where the distance from the root of the lobe to the pleura was not great. This interstitial process was particularly conspicuous about the vessels and involved both arteries and veins (Figs. 11, 13, 14, and 15). The peribronchial process (Fig. 12), always less conspicuous than the perivascular one, was usually most extensive in the tissue lying between the bronchus and its accompanying pulmonary artery, this relation being maintained throughout the course of the bronchi to the terminal bronchioles (Fig. 15). The leucocytic infiltration was composed largely of polymorphonuclear leucocytes. Large mononuclear cells and lymphocytes, however, were always present. In a few cases a considerable degree of hemorrhage in the perivascular and peribronchial tissue was found. Fibrin was also present. Necrosis of the tissue was not encountered. The perivascular, peribronchial, and septal lymphatics were distended and often contained large numbers of leucocytes (Figs. 16, 17, and 23).

The epithelium of the bronchi and bronchioles appeared comparatively intact. The bronchi and bronchioles contained little or no exudate (Fig. 15). The vessels and the capillaries of the alveolar walls were greatly engorged (Fig. 18). In the parenchymal tissue

proximal to the hilum the walls of the alveolar ducts and of the adjacent alveoli were often swollen and infiltrated with polymorphonuclear leucocytes, variable numbers of large mononuclear cells, and occasional lymphocytes (Figs. 22 and 23). Some of the alveoli in these areas contained a few large mononuclear cells which appeared to be desquamated alveolar epithelium; otherwise they contained no exudate.

Red Hepatization.—With the further progress of the disease to the stage of red hepatization the more familiar histological pictures of lobar pneumonia appeared. Exudation into the alveoli occurred first in the parenchymal tissue proximal to the hilum, and subsequently progressively involved the more distal portions. In the earliest stages of hepatization the alveoli contained coagulated serum, and the alveolar walls frequently were infiltrated with polymorphonuclear leucocytes and large mononuclear cells. In areas where hepatization was somewhat more advanced the alveoli contained variable numbers of polymorphonuclear leucocytes, large mononuclear cells, and red blood corpuscles embedded in a network of fibrin (Figs. 25, 27, and 28). Frequently the large mononuclear cells contained phagocytosed leucocytes or red blood corpuscles. The character of the mononuclear cells in the exudate and the fact that similar cells were present in considerable numbers in the bronchial walls, perivascular tissue, and alveolar walls during the stage of engorgement, indicate that they were probably, at least in large part, endothelial leucocytes. Some, however, appeared to be desquamated, alveolar epithelial cells.

The number of red blood corpuscles in the exudate varied greatly in different cases and in different areas in the same case. The almost complete absence of red blood corpuscles in the alveolar exudate in some cases in the stage of red hepatization makes it probable that the color of the lung in this stage is largely due to the greatly congested alveolar capillaries.

The interstitial lesions so prominent during the stage of engorgement, though still present in the stage of red hepatization, were much less conspicuous where hepatization had occurred. At the margins of the advancing pneumonic consolidation, however, the primarily interstitial character of the lesion was clearly evident, the peri-

bronchial and perivascular tissue and the alveolar walls being edematous and infiltrated with leucocytes to a variable extent. The lumina of terminal bronchioles and alveolar ducts in many places were still free from exudate, in others where red hepatization was well advanced they contained an exudate similar to that found in the alveoli.

Gray Hepatization.—With still further advance of the process the number of polymorphonuclear leucocytes in the alveolar exudate increased, the fibrin threads often became granular and degenerated, the congestion of the alveolar capillaries disappeared, and the picture passed to that of typical gray hepatization.

The transition from red to gray hepatization occurred first in the portions of the lobe where red hepatization first developed; that is, in the parenchymal tissue proximal to the hilum. Subsequently the more distal portions of the lobe assumed the appearance of gray hepatization. In this stage the alveoli were filled with masses of polymorphonuclear leucocytes. Small numbers of large mononuclears, lymphocytes, and red blood corpuscles were also present. The alveolar walls were thin and appeared well preserved, their capillaries being no longer engorged (Fig. 29). The alveolar ducts and terminal bronchioles were filled with an exudate of leucocytes, red blood corpuscles, and fibrin, and the bronchi contained a variable amount of polymorphonuclear leucocytes and granular debris. The epithelium of the bronchioles and bronchi appeared comparatively intact. Necrosis of the alveolar structure or of the bronchial walls was not found. Edema and leucocytic infiltration of the peribronchial and perivascular tissue, though still present to some extent, were much less conspicuous than in the earlier stages of the disease. The pleura was covered with a dense exudate of fibrin in which polymorphonuclear leucocytes were embedded.

Resolution.—The picture of gray hepatization passed progressively to that of resolution without sharp demarcation between them. In monkeys which died late in the disease or were killed shortly after recovery the alveolar exudate was undergoing rapid disintegration and consisted of leucocytic, nuclear elements and granular debris, occasional lymphocytes, and red blood corpuscles. The alveolar epithelium showed active proliferation and desquamation. As the

process of resolution progressed, desquamated epithelial cells were frequently the predominating cells in the alveoli, the preceding exudate having largely disappeared (Fig. 30). The bronchioles and bronchi were filled with polymorphonuclear leucocytes, mononuclear cells, and desquamated alveolar epithelium in varying proportions. The peribronchial and perivascular tissue was again conspicuous, being infiltrated with large numbers of lymphocytes and plasma cells, and to some extent with polymorphonuclear leucocytes. In still later stages of resolution the alveoli were largely devoid of exudate, containing only here and there a few desquamated epithelial cells. The bronchi and bronchioles no longer showed exudate in their lumina. The perivascular and peribronchial tissue was still conspicuously infiltrated with plasma cells and lymphocytes.

Organization.—Coincident with resolution a variable degree of organization was always found. This was consistently present in the perivascular tissue, though varying greatly in extent, even when complete resolution of the alveolar exudate had taken place. New connective tissue formation about the bronchi also occurred to a considerable extent in cases which showed a widespread organizing pneumonia. Organization of the alveolar exudate, when it occurred, was usually of patchy distribution, alveoli filled with plugs of young connective tissue lying side by side with those in which resolution was rapidly progressing (Fig. 31). The masses of organizing alveolar exudate were covered by a thin layer of epithelium apparently derived from the alveolar walls. In three cases a very extensive organizing pneumonia was found, the normal structure of the lung parenchyma being replaced by young connective tissue in which the distorted remains of alveoli might here and there be found (Fig. 32). The pleural exudate was undergoing organization.

In the following paragraphs autopsy protocols illustrating the different stages of the disease are presented.

PROTOCOLS.

Protocol 1.—Monkey 98. *Macacus syrichtus*, male; weight 4,100 gm. May 20, 1919. Intratracheal injection of 0.000001 cc. of Pneumococcus Type I. Developed pneumonia with severe pneumococcus septicemia and died on May 23.

Anatomical Diagnosis.—Lobar pneumonia, left upper, left lower, right upper, and right lower lobes; stage of engorgement.

Pleural cavities.—Contain no fluid. Pleural surfaces are for the most part glistening, but in scattered patches over the upper and lower lobes appear dull. There is no evident deposit of fibrin. *Right lung.*—Somewhat collapsed. The upper lobe feels soggy in its posterior portion, but shows no consolidation. The posterior and inferior surfaces present blotchy dark red areas extending outward from the hilum toward the periphery. The cut surface appears intensely congested and yields a moderate amount of blood-tinged frothy fluid. The walls of the larger vessels and bronchi appear edematous. The alveoli are air-containing. The lower lobe presents a similar picture, the upper, posterior, and external surfaces showing deep red, blotchy areas extending from the hilum toward the periphery. The cut surface shows marked congestion and yields a moderate amount of fluid. The walls of the larger vessels and bronchi appear edematous. The alveoli are air-containing. The bronchi contain a small amount of blood-tinged mucus. The middle lobe is pale pink and crepitant throughout. *Left lung.*—The upper and lower lobes show an involvement similar in character to that found on the right. There is no consolidation. The left middle lobe appears normal. *Bronchial lymph nodes.*—Enlarged and soft; pinkish gray in color. *Other organs.*—Pericardium and heart show no changes. Liver and kidneys show cloudy swelling.

Cultures.—Heart's blood, bronchi, and left lower lobe, Pneumococcus Type I.

Macroscopic Examination.—Examination of a large histological section from the right lower lobe (Fig. 4) shows marked thickening of the perivascular tissue. This is particularly conspicuous about the larger arteries and veins near the hilum, but is also present about the smaller vessels in the more peripheral portions of the lobe. The walls of the large and medium sized bronchi are similarly thickened, though much less conspicuously so. The bronchi and bronchioles contain no exudate. Many of the interlobular septa appear moderately thickened. The alveoli are air-containing.

Microscopic Examination.—Right upper lobe.—The pleura in sections near the root of the lobe shows capillary engorgement, moderate edema, and infiltration with polymorphonuclear leucocytes, large mononuclear cells, and occasional lymphocytes. This process is especially prominent at the junction of interlobular septa with the pleura. The pleural surface appears intact and there is no fibrinous exudate. The adventitia of the veins and arteries is greatly distended with edema and intensely infiltrated with polymorphonuclear leucocytes and varying numbers of large mononuclear cells and lymphocytes. This process is most conspicuous about the larger vessels, but is also present about the smaller vessels throughout the lobe (Figs. 13 and 14). The perivascular lymphatics are greatly distended and filled with leucocytes (Fig. 17) which in places are embedded in fibrin. The interlobular septa are edematous and infiltrated with abundant polymorphonuclear leucocytes, moderate numbers of large mononuclear cells, and occasional lymphocytes (Fig. 16). Their lymphatics are distended and filled with leucocytes. The walls of the larger bronchi near the root of the lobe

are edematous and infiltrated with leucocytes (Fig. 12). The walls of the smaller bronchi and bronchioles show little or no edema and only moderate leucocytic infiltration (Fig. 15). The epithelium of the bronchi and bronchioles appears intact. The bronchioles contain no exudate. In some of the larger bronchi a few polymorphonuclear leucocytes are seen penetrating between the epithelial cells. The alveoli contain no exudate, except here and there a few large mononuclear cells. The alveolar capillaries are intensely engorged (Fig. 18). Where the engorgement is most extreme the alveoli often appear atelectatic. The alveolar walls show no leucocytic infiltration, except in a few places adjacent to the vessels or bronchi. Moderate numbers of pneumococci are seen in the perivascular and peribronchial tissue, some free, others within polymorphonuclear leucocytes. Occasional pairs are seen in the interlobular septa, in the pleura, and in alveolar walls adjacent to the larger vessels. A few are entangled in the cilia of the epithelium of the larger bronchi. None are seen in the smaller bronchi, bronchioles, or alveolar spaces. *Right lower lobe.*—Presents a similar picture. *Left lung.*—Sections closely resemble those from the right lung. *Bronchial lymph nodes.*—The marginal lymph sinuses are filled with large mononuclear phagocytes, many of which contain polymorphonuclear leucocytes. Many lymphocytes and a few polymorphonuclear leucocytes are also present. No pneumococci are seen.

Protocol 2.—Monkey 23. *Macacus syrichtus*, male; weight 3,555 gm. Mar. 18, 1919. Intratracheal injection of 1 cc. of Pneumococcus Type I. Developed pneumonia with pneumococcus septicemia and terminal leucopenia. Mar. 23, 1 a.m. Died.

Anatomical Diagnosis.—Lobar pneumonia, left lower lobe, red hepatization; right lower lobe, engorgement; acute fibrinous pleuritis, left.

Left pleural cavity.—Contains no fluid. There is a thin layer of fresh fibrin over the posterior and external surfaces of the left lower lobe. *Right pleural cavity.*—Contains no fluid. Pleura is smooth and glistening. *Left lung.*—The posterior two-thirds of the left lower lobe from the hilum nearly to the base is firmly consolidated, the surface dark red in color. The anterior portion is crepitant and air-containing. On section the consolidated portion is dark red and finely granular, the alveoli being filled with plugs of exudate. The base and anterior portions are congested, and yield a considerable amount of bloody, frothy fluid. The perivascular tissue appears edematous. The interlobular septa are not prominent. The bronchi contain a moderate amount of bloody mucoid material. The upper and middle lobes are pale pink and crepitant. *Right lung.*—The upper and posterior surfaces of the lower lobe are mottled with deep red patches. The cut surface shows congestion and moderate edema at the root of the lobe. There is no consolidation. The upper and middle lobes appear normal. *Bronchial lymph nodes.*—Enlarged and soft; pinkish gray in color. *Bone marrow of femur.*—Pale pinkish yellow. *Other organs.*—Pericardium and heart show no abnormalities. Liver and kidneys show cloudy swelling.

Cultures.—Heart's blood, left lower lobe, and spleen, Pneumococcus Type I.

Microscopic Examination.—Left lower lobe.—The pleura is edematous and infiltrated with moderate numbers of polymorphonuclear leucocytes, large mononuclear cells, and occasional lymphocytes. There is a thin meshwork of fibrin on the surface. Sections from the consolidated portion of the lobe show the alveoli uniformly filled with polymorphonuclear leucocytes, moderate numbers of large mononuclear cells, and fibrin. Some contain many red blood corpuscles, others none. The leucocytes are for the most part well preserved; the large mononuclear cells frequently contain phagocytosed leucocytes. The alveolar walls show little or no leucocytic infiltration; the alveolar capillaries are engorged. The adventitia of the arteries and veins is moderately edematous and is infiltrated with many large mononuclear phagocytes and lymphocytes. A few polymorphonuclear leucocytes and an occasional plasma cell are also seen. The perivascular lymphatics are filled with similar cells. The walls of the bronchi and bronchioles are infiltrated with large mononuclear cells, lymphocytes, and moderate numbers of polymorphonuclear leucocytes, their lymphatics being filled with similar cells. The epithelium appears intact; the lumina contain a variable amount of exudate consisting of leucocytes, red blood corpuscles, and fibrin. Sections at the margin of the consolidated area show the alveoli irregularly filled with exudate (Fig. 25). In some, large mononuclear phagocytic cells predominate, in others, the exudate consists almost entirely of red blood corpuscles, while in others, polymorphonuclear leucocytes are abundant. Many contain coagulated serum and fibrin with comparatively little cellular exudate. The alveolar capillaries are intensely engorged. Surrounding this area is a zone in which the alveoli contain only serum and occasional desquamated epithelial cells. The alveolar walls show some infiltration with polymorphonuclear leucocytes and large mononuclear cells. The perivascular tissue is conspicuously infiltrated. The bronchioles contain little or no exudate. Few pneumococci are seen in the consolidated portion of the lobe and, for the most part, they stain poorly and are contained within polymorphonuclear leucocytes of the alveolar exudate. None are seen in the perivascular or peribronchial tissue. At the margins of the consolidated area, however, they are quite numerous in the alveolar exudate and stain well. In the surrounding zone of edematous alveoli they are present both in the serous exudate and in the alveolar walls (Fig. 26); while in the anterior portions of the lobe, where exudation into the alveoli has not occurred, they are seen only in the alveolar walls lying between the capillary and the epithelium lining the alveoli. *Bronchial lymph nodes.*—The marginal lymph sinuses are filled with numerous large mononuclear cells, many of which show inclusions of polymorphonuclear leucocytes and red blood corpuscles. Moderate numbers of lymphocytes, polymorphonuclear leucocytes, and red blood corpuscles are also present (Fig. 33). *Bone marrow of femur.*—Largely devoid of blood cells (Fig. 34). A few myelocytes, lymphocytes, immature polymorphonuclear leucocytes, and megaloblasts are scattered through the tissue or aggregated in small clumps. Groups of normoblasts and an occasional megalocaryocyte are also seen.

Protocol 3.—Monkey 26. *Macacus syrichtus*, male; weight 2,680 gm. Mar. 21, 1919. Intratracheal injection of 1 cc. of Pneumococcus Type I. Developed pneumonia. Killed on 9th day while still sick. Leucocytosis at time of death.

Anatomical Diagnosis.—Lobar pneumonia, right and left lower lobes; stage of gray hepatization; acute fibrinous pleuritis, bilateral.

Left pleural cavity.—Contains no fluid; there are fresh fibrinous adhesions between the visceral and parietal pleuræ over the left lower lobe. *Right pleural cavity.*—Contains no fluid; there is a fresh fibrinous exudate on the posterior and external surfaces of the right lower lobe. *Left lung.*—There is a massive and uniform consolidation of the left lower lobe involving the entire lobe except the anterior margin which is crepitant. The cut surface is uniformly yellowish gray, finely granular, and comparatively dry. The bronchi and bronchioles are not prominent, but contain a moderate amount of exudate. The upper and middle lobes are collapsed, pale pink, and crepitant throughout. *Right lung.*—The lower lobe shows a massive consolidation similar in all respects to that on the left. The cut surface presents the typical appearance of gray hepatization. *Bronchial lymph nodes.*—Enlarged and succulent. *Bone marrow of femur.*—Of normal consistency; yellowish pink in color. *Other organs.*—Pericardium normal. Heart appears moderately dilated, but otherwise normal. Liver and kidneys show cloudy swelling.

Cultures.—Heart's blood and lungs, no growth; bronchus, Pneumococcus Type I.

Microscopic Examination.—Left lower lobe.—The pleura is thickened and infiltrated with large numbers of polymorphonuclear leucocytes. The lining pleural cells are well preserved. The pleura is covered with a dense meshwork of fibrin infiltrated with leucocytes. The alveoli, except at the extreme margins of the lobe, are uniformly filled with an exudate of polymorphonuclear leucocytes and fibrin (Fig. 29). A few large mononuclear phagocytic cells and lymphocytes are also seen. The alveolar walls are thin and show little or no leucocytic infiltration. The alveolar capillaries are compressed and empty. The leucocytes of the alveolar exudate are for the most part well preserved, but in portions of the lobe the alveolar exudate is undergoing disintegration, and there is considerable proliferation and desquamation of alveolar epithelium. The adventitia of the vessels, though not distended with edema, is infiltrated with polymorphonuclear leucocytes and moderate numbers of large mononuclear cells and lymphocytes. There is no new connective tissue formation. The walls of the bronchi and bronchioles do not appear thickened, but are everywhere infiltrated with a few polymorphonuclear leucocytes, large mononuclear phagocytes, and lymphocytes. The epithelium is well preserved except for occasional places where desquamation has occurred. The alveolar ducts, terminal bronchioles, and bronchi are filled with an exudate of leucocytes and fibrin. The perivascular and peribronchial lymphatics, though not conspicuously distended, contain many polymorphonuclear leucocytes and moderate numbers of large

mononuclear cells and lymphocytes. The interlobular septa are not conspicuous. In the peripheral alveoli near the pleura the exudate is less compact and frequently shows a preponderance of large mononuclear phagocytic cells with inclusions of leucocytes. The alveolar walls are greatly thickened by infiltration with polymorphonuclear leucocytes. The perivascular tissue is conspicuous and shows a dense leucocytic infiltration, the perivascular lymphatics being filled with leucocytes. Pneumococci are very scanty in the alveolar exudate and when seen stain poorly or are phagocytosed. In the anterior margin where consolidation has not occurred many are seen in the alveolar walls or in the coagulated serum in the alveoli. *Bone marrow of femur.*—Shows a marked cellular hyperplasia. All types of hematopoietic cells are present in abundance, mature forms being very numerous (Fig. 35).

Protocol 4.—Monkey 89. *Macacus syrichtus*, male; weight 2,462 gm. May 20, 1919. Intratracheal injection of 0.001 cc. of Pneumococcus Type I. Developed pneumonia and recovered by crisis on May 31. June 4. Killed.

Anatomical Diagnosis.—Lobar pneumonia, right lower lobe; stage of resolution; organizing pleuritis, right.

Left pleural cavity.—Contains no fluid; pleural surfaces glistening. *Right pleural cavity.*—Contains no fluid; the lower portion is obliterated by moderately firm adhesions between the parietal and visceral pleuræ. *Left lung.*—Collapsed, pale pink, and crepitant throughout. *Right lung.*—The lower lobe presents a translucent gray appearance. It is moderately firm throughout but of a doughy consistency. The cut surface presents a fairly uniform pinkish gray gelatinous appearance. The bronchi contain a small amount of mucoid material. The upper and middle lobes are pale pink and crepitant throughout.

Cultures.—Heart's blood and right lower lobe, no growth.

Microscopic Examination.—Right lower lobe.—The pleura is covered with a layer of moderately vascular granulation tissue, the interstices of which are infiltrated with numbers of lymphocytes and occasional large mononuclear cells, polymorphonuclear leucocytes, and plasma cells. The pleural lymphatics are filled with similar cells. The alveoli are almost uniformly filled with a pink-staining finely granular material (Fig. 30). The majority contain many large round or oval mononuclear cells with faint staining, sometimes vacuolated protoplasm. A few of these cells contain inclusions of polymorphonuclear leucocytes or red blood corpuscles. Occasional larger multinucleated cells of similar structure are seen. Moderate numbers of lymphocytes are present and an occasional polymorphonuclear leucocyte or red blood corpuscle is also seen. The alveolar epithelium shows active proliferation in many places. The alveolar walls are not infiltrated, their capillaries not engorged. An occasional alveolus contains a plug of organizing exudate. The adventitia of the vessels is conspicuously infiltrated with lymphocytes, moderate numbers of plasma cells, and occasional polymorphonuclear leucocytes. There is a moderate degree of new connective tissue formation about most of the vessels. The walls of the bronchi

and bronchioles are similarly though less conspicuously infiltrated. The lumina contain a small amount of granular material and a few large mononuclear cells similar to those in the alveoli. No pneumococci are seen.

Protocol 5.—Monkey 64. *Macacus syrichtus*, female; weight 2,600 gm. May 6, 1919. Intratracheal injection of 0.000001 cc. of Pneumococcus Type I. Developed pneumonia; improving May 13, but continued to run an irregular fever until June 2. June 4. Appeared well. Killed.

Anatomical Diagnosis.—Lobar pneumonia, left lower lobe; organization; fibrous pleuritis, left.

Left pleural cavity.—Contains no fluid; the lower portion is obliterated by moderately firm fibrous adhesions. *Right pleural cavity.*—Contains no fluid; pleural surfaces glistening. *Left lung.*—The lower lobe is firmly consolidated throughout, of translucent gray color, and rubber-like consistency. The cut surface is light gray, dry, and studded with fine, firm granulations. The vessels, bronchi, and interlobular septa are prominent. The upper and middle lobes are pale pink and crepitant. *Right lung.*—Voluminous, pale pink, and crepitant throughout.

Cultures.—Heart's blood, no growth; left lower lobe, four colonies of Pneumococcus Type I; left main bronchus, Pneumococcus Type I.

Microscopic Examination.—Left lower lobe.—The peribronchial and perivascular tissue and the interlobular septa are everywhere greatly thickened by the formation of new connective tissue, the interstices of which are infiltrated with many lymphocytes and plasma cells. In places polymorphonuclear leucocytes are also present. The alveolar walls are similarly affected in many parts of the section, in other places they show no organization. In some areas the process of organization is so extensive that only the distorted and compressed outlines of the alveoli remain. Organization and resolution of the alveolar exudate are going on side by side in adjacent alveoli (Fig. 31). Some alveoli contain numerous desquamated epithelial cells, together with a few lymphocytes and occasional polymorphonuclear leucocytes, in a groundwork of amorphous material. The alveolar epithelium shows very active and widespread proliferation. Other alveoli are filled with plugs of new connective tissue infiltrated with lymphocytes and plasma cells. These plugs are covered with an epithelial layer, the epithelial cells sometimes being cuboidal, sometimes thin and flattened out. A few small groups of alveoli filled with polymorphonuclear leucocytes are also seen. The alveolar ducts and many of the terminal bronchioles are filled with masses of new connective tissue similar to those in the alveoli. The bronchial epithelium appears intact. The bronchi contain polymorphonuclear leucocytes, lymphocytes, and desquamated alveolar epithelial cells in a groundwork of amorphous material.

Pathogenesis of Lobar Pneumonia.

Although the pathology of lobar pneumonia has been well known for many years, little definite knowledge concerning the pathogenesis of the disease has developed. Two principal theories with respect to the initial mode of infection have existed. Some writers[3] have advocated the theory that lobar pneumonia is hematogenous in origin, basing this belief on the fact that pneumococci have been isolated from the blood prior to the development of symptoms or physical signs of pneumonia. This point of view, however, has received no experimental support, since attempts to produce lobar pneumonia in animals by intravenous inoculation of pneumococci have consistently failed.[4, 5, 6] On the other hand, the more commonly accepted view that the mode of infection is by way of the air passages has received a certain amount of confirmation in the experimental production of pneumococcus pneumonia in animals by various methods of intratracheal or intrabronchial inoculation.[1, 6–9] However, these experiments have not been conclusive, either because the pneumonia produced was not clearly lobar pneumonia or because the method of inoculation or amount of culture material injected tended to vitiate the value of the experiments.

Knowledge concerning the initial point of invasion of the lung by the pneumococcus, the character and location of the primary lesions, and the method by which the infection spreads throughout the lung would appear to be equally doubtful, if one may judge by the indefiniteness with which these subjects are presented in standard textbooks of pathology. Even in the later stages, although it is generally recognized that hepatization in lobar pneumonia is a progressive process, there still remains a difference of opinion as to whether consolidation begins at the periphery and extends centrally or *vice versa*.

[3] Kidd, P., *Lancet*, 1912, i, 1589.
[4] Wadsworth, A., *Am. J. Med. Sc.*, 1904, cxxvii, 851.
[5] Rasquin, E., *Arch. méd. exp. et anat. path.*, 1910, xxii, 804.
[6] Armstrong, R. R., *Brit. Med. J.*, 1914, ii, suppl., 57.
[7] Lamar, R. V., and Meltzer, S. J., *J. Exp. Med.*, 1912, xv, 133.
[8] Wollstein, M., and Meltzer, S. J., *J. Exp. Med.*, 1912, xvi, 126.
[9] Winternitz, M. C., and Hirschfelder, A. D., *J. Exp. Med.*, 1913, xvii, 657.

Review of the literature reveals a striking paucity of attempts to answer these questions by experimental procedures. Papers by Müller[10] and by Rasquin[5] are of particular interest. Müller undertook a study of the pathogenesis of aspiration pneumonia experimentally produced in rabbits by vagotomy. He showed that bacteria-bearing material aspirated from the mouth had penetrated as far as the terminal bronchioles by the end of 6 hours. By 8 hours evidence of bacterial infection was present. The walls of alveoli lying adjacent to the alveolar ducts in which affected bronchioles terminated were swollen and infiltrated with leucocytes, and there were epithelial desquamation and beginning exudation into these alveoli, but the alveolar ducts, atria, and alveoli to which the affected bronchioles led were free from exudate. Bacteria were seen in the infiltrated alveolar walls and in the adjacent alveoli, but not in those with which the affected terminal bronchioles communicated. Still later with wider extension of the process the bacteria were found spreading in the lymph channels of the interstitial framework of the lung and in the alveolar walls, exudation and passage of bacteria into the alveolar spaces occurring only after bacterial invasion of the alveolar walls had occurred. From these observations he inferred that the bacteria gained entrance into the pulmonary tissue at the point where the cuboidal epithelium of the terminal bronchiole gives place to the flattened epithelium of the alveolar duct and atrium, and that the invasion was facilitated by the mechanical injury caused by the aspirated foreign material. He established the fact that further spread of the infection was by way of the interstitial tissue of the lung framework and by way of the alveolar walls.

Rasquin showed that in pneumonia experimentally produced in rabbits by the intratracheal injection of attenuated pneumococci, consolidation invariably occurred in the portions of the lobe proximal to the hilum and usually in the posterior half, the distal portions being free from consolidation. Since the rabbits died with pneumococcus septicemia in a comparatively short time complete lobar consolidation was not found and he considered the process comparable with catarrhal rather than with lobar pneumonia.

In the present study of lobar pneumonia experimentally produced in monkeys by the intratracheal injection of pneumococcus, the attempt has been made to determine the following points concerning the pathogenesis of the disease: (1) whether lobar pneumonia is a bronchiogenic or a hematogenous infection; (2) at what point or points the pneumococcus primarily invades the lung tissue; (3) what the character and location of the initial lesions are; (4) by what paths the pneumococci spread from the initial points of invasion to the remainder of the lobe; and (5) whether hepatization begins more or less simultaneously throughout a lobe or whether it begins centrally and spreads peripherally, or *vice versa*.

[10] Müller, W., *Deutsch. Arch. klin. Med.*, 1902, lxxiv, 80.

Initial Path of Infection.—It has been stated in the preceding paper[1] that pneumonia was consistently produced in normal monkeys by the intratracheal injection of pneumococcus, and it was shown that the pneumonia so produced ran a clinical course identical with that of lobar pneumonia in man. It was furthermore stated that attempts to produce pneumonia by subcutaneous or intravenous inoculation consistently failed. This was equally true of normal monkeys and of monkeys whose resistance to pneumococcus infection had been increased by preliminary inoculations with pneumococcus vaccine. It was also shown that pneumococci may enter the blood stream following intratracheal injection, in some instances before the symptoms or physical signs of pneumonia have developed. It therefore seems safe to conclude that lobar pneumonia is a bronchiogenic and not a hematogenous infection.

Site of Primary Invasion of the Lung Tissue.—It is conceivable that the pneumococcus may primarily invade the lung tissue early in the course of the bronchi by penetration of the bronchial mucous membrane, or that it may pass down the lumina of the bronchi to the terminal bronchioles, and there penetrate the epithelium, or that it may be carried still further and invade the lung tissue only after it has gained access to the alveolar ducts, atria, or alveoli. In an attempt to answer this question a monkey was injected intratracheally with the growth in 10 cc. of an 18 hour broth culture of pneumococcus thrown down by centrifuge and resuspended in 1.5 cc. of the supernatant broth. 3 hours after injection the monkey was killed and autopsy immediately performed. The protocol follows.

Protocol 6.—Monkey 72. *Macacus syrichtus*, female. Apr. 23, 1919, 11 a.m. Intratracheal injection of 10 cc. (in 1.5 cc.) of 18 hour broth culture of Pneumococcus Type I. 2 p.m. Killed.

Autopsy.—Pleural cavities.—Contain no fluid; pleural surfaces glistening. *Left lung.*—Pale pink and air-containing throughout. No edema or congestion. *Right lung.*—The lower lobe shows an edematous appearing area at the root, the cut surface yielding a moderate amount of fluid. There is no congestion. The remainder of the lobe and the upper and middle lobes appear normal. The larger bronchi contain a moderate amount of frothy fluid. The smaller bronchi are empty. *Lymph nodes.*—Nodes at the hilum appear moderately enlarged. *Other organs.*—Show nothing of importance.

Bacteriology.—Stained films from trachea and right main bronchus show many pneumococci; the bronchial exudate also shows moderate numbers of polymor-

phonuclear leucocytes. There is no phagocytosis. *Cultures.*—Heart's blood, Pneumococcus Type I; trachea, Pneumococcus Type I; right main bronchus, Pneumococcus Type I; left main bronchus, no growth; small bronchi in right and left lower lobes, no growth.

Microscopic Examination.—Right lower lobe.—In sections cut close to the hilum the perivascular and peribronchial tissue is edematous and infiltrated with polymorphonuclear leucocytes. The interlobular septa and portions of the pleura are similarly affected. The walls of the smaller bronchi and terminal bronchioles and of their accompanying arteries are densely infiltrated with leucocytes. The walls of the alveolar ducts, atria, and adjacent alveoli are likewise infiltrated (Fig. 22). The epithelium of the large bronchi shows active secretion of mucus but otherwise appears intact in most places. At a number of points, however, the epithelium is injured, and here many polymorphonuclear leucocytes are seen passing into the lumen of the bronchus where they are accumulated in masses on the surface. The bronchioles, alveolar ducts, and atria contain no exudate except in a few instances where the process is well advanced. The alveoli are free from exudate and often appear atelectatic. Moderate numbers of pneumococci are seen entangled in the cilia of the bronchial epithelium or in the mucus secretion. At the points where the bronchial epithelium shows injury pneumococci are seen penetrating the bronchial wall (Fig. 19). Small numbers of pneumococci are seen in the margins of the peribronchial and perivascular tissue, apparently largely in the lymphatics. Pneumococci are more numerous in the walls of the smaller bronchi and vessels, and some are seen in the interlobular septa and affected portions of the pleura. They are present in considerable numbers in the walls of the terminal bronchioles, alveolar ducts, and atria. In the alveolar walls lying adjacent to the vessels, the interlobular septa, and especially the alveolar ducts, they are very abundant, apparently lying between the capillaries and the lining epithelium. None are seen in the lumina of the terminal bronchioles, alveolar ducts, or alveoli, except in a few places where the lesion is well advanced and exudation into the alveoli or alveolar ducts has occurred. In sections from more distal portions of the lobe the tissue appears normal and no pneumococci are seen. *Right upper lobe.*—Sections adjacent to the hilum show a similar picture to that found in the lower lobe. *Other lobes.*—No abnormalities are shown and no pneumococci are seen. *Bronchial lymph node.*—The marginal sinus is crowded with large numbers of polymorphonuclear leucocytes and a few large mononuclear cells and lymphocytes. An occasional free or phagocytosed pneumococcus is seen. *Trachea.*—Appears normal except for a moderately excessive mucus secretion. A few pneumococci are seen entangled in the cilia of the epithelium.

In attempting to form any certain opinion from the results of this experiment as to where the pneumococcus primarily invades the lung tissue, it is obvious that a considerable degree of conservatism is

necessary, since the number of pneumococci injected was very large and since considerable invasion of the tissue had already occurred at the time the animal was killed. It at least may be stated with reasonable positiveness that the initial invasion occurs somewhere comparatively close to the hilum. That it occurred in this case, in part at least, by direct penetration of pneumococci into the walls of the large bronchi is clear. Whether pneumococci had passed down the lumina of the bronchi to the terminal bronchioles or even further into the alveolar ducts and alveoli of the portion of the lobe proximal to the hilum and there invaded the lung tissue is uncertain. It seems doubtful, however, in view of the fact that no pneumococci were found in the lumina of the bronchioles, alveolar ducts, and alveoli, except in a few places where the lesion was well advanced, while on the other hand they were very numerous in the walls of these structures where the process was early and no exudation into the bronchioles or alveoli had occurred. That this practical absence of pneumococci in the terminal bronchioles and alveoli was found in spite of the very large numbers of pneumococci injected lends confirmation to this doubt. The evidence, though strongly against the latter mode of invasion, does not, however, certainly exclude it.

Character and Location of the Initial Lesions.—Opportunity to study the earliest lesions of lobar pneumonia before hepatization had begun was presented in Monkeys 17, 88, 98, 101, 109, and 114, all of which died in the stage of engorgement. The protocol of Monkey 98 has been presented above and is representative of the group. Since all these monkeys, except Monkey 17, were inoculated with minute amounts of pneumococcus culture, such as may be assumed to be reasonably comparable with the probable infecting dose in man, the picture encountered may safely be considered to be that of the earliest stages of lobar pneumonia in man.

Histological sections from all these animals showed clearly that the primary lesions were of the interstitial framework of the lung with accompanying involvement of the lymphatic system. These lesions have been presented in detail above and need no further description. The earliest alveolar lesions beside capillary engorgement were likewise interstitial in character, consisting in leucocytic infiltration of the alveolar walls before exudation into the alveoli

occurred. This took place primarily in the walls of alveoli lying adjacent to terminal bronchioles and alveolar ducts of the central portions of a lobe and to a variable extent in the walls of alveoli lying adjacent to the larger bronchi and vessels.

That the primary lesion of lobar pneumonia is one of the interstitial framework of the lung was well illustrated in Monkeys 96 and 107, which had abortive attacks with recovery on the 3rd and 4th days respectively. Autopsies showed a purely interstitial pneumonia without further advance of the process to the stage of hepatization (Fig. 10).

Spread of the Pneumococci from the Initial Points of Invasion to the Remainder of the Lobe.—This point was readily determined by study of the distribution of pneumococci in the lungs of monkeys dying in the stage of engorgement. As described in the protocols of Monkeys 98 and 72, pneumococci were found in the interstitial tissue and lymphatics of the lung, but were not present in the lumina of the bronchioles, alveolar ducts, or atria, or in the alveolar spaces. In detail, they were present in the perivascular tissue and bronchial walls (Figs. 20 and 21), in the interlobular septa and pleura, in the walls of the terminal bronchioles and alveolar ducts, and in the walls of alveoli lying adjacent to these structures. In more advanced cases of pneumonia in which partial hepatization of a lobe had occurred, a similar interstitial distribution of pneumococci was found in the peripheral unconsolidated portions (Fig. 24). Where beginning exudation had occurred into the alveoli pneumococci were found both in the alveolar walls and in the exudate (Fig. 26). Where hepatization was fully developed they were present in variable numbers in the exudate, often largely phagocytosed or staining poorly, and they were no longer present in the alveolar walls.

It is quite clear, therefore, that invasion and spread of pneumococci in the lung in lobar pneumonia is by way of the perivascular, peribronchial, and septal tissue and lymphatics, and that the alveolar structure is primarily infected by spread of the pneumococci from the grosser framework of the lungs into the alveolar walls. With further advance of the process to the stage of hepatization pneumococci pass out from the alveolar walls into the alveolar spaces together with the exudate.

Development of Hepatization.—It has been stated above and illustrated by the protocol of Monkey 23 that in monkeys which died early in the stage of hepatization the consolidated areas were found invariably to occupy the portions of the lobe proximal to the hilum, while the more distal portions of the lobe were still air-containing (Fig. 8). Although by no means an absolute rule, hepatization usually occurred first in the posterior and upper parts of the lower lobes, in the lower parts of the middle lobes, and in the lower and posterior parts of the upper lobes. This distribution in no way precluded early extension of the consolidation as far as the pleura, since the pleura is comparatively near the large bronchi and vessels in the part of the lobe proximal to the hilum. As the disease progressed hepatization spread to the distal portions of the lobe until complete or nearly complete lobar consolidation had occurred (Fig. 9). As in lobar pneumonia in man, the anterior margins frequently remained air-containing.

Whether a definite lobular arrangement of the exudate might be recognized in the early stages of hepatization has been impossible to determine. It seems possible that a certain amount of variation exists in this respect, depending upon the rapidity with which pneumococci are distributed throughout the lung and the rapidity with which hepatization develops.

Although it seems reasonable to conclude from the study of the development of hepatization in lobar pneumonia in monkeys that consolidation in lobar pneumonia in man begins centrally and spreads peripherally, this does not preclude the probability that in a rapidly spreading pneumococcus invasion of the lung hepatization of an entire lobe may occur within a comparatively short time, nor does it preclude the possibility that in fairly resistant individuals the infection might at first be limited to the interstitial framework in the central portions of the lobe with the primary development of hepatization in the peripheral portions where the framework is less dense. In the latter case, the picture would approach that of a lobular pneumonia or at most a lobar pneumonia of limited involvement.

SUMMARY.

Study of the pathology of pneumonia experimentally produced in monkeys by the intratracheal injection of pneumococcus has shown that it is identical with the pathology of lobar pneumonia in man. It has been found that the pneumococcus primarily invades the pulmonary tissue at some point or points in the portion of the lobe proximal to the hilum, that it spreads rapidly throughout the lobe by way of the perivascular, peribronchial, and septal interstitial tissue and lymphatics, quickly reaching the pleura, and that it invades the alveolar structure primarily by way of the alveolar walls, subsequently passing into the alveolar spaces simultaneously with the outpouring of exudate into the alveoli. It has been shown that the initial mode of invasion may be by direct penetration at one or more points into the walls of the larger bronchi near the hilum. The possibility that primary invasion may occur in terminal bronchioles, alveolar ducts, or alveoli of the parenchyma near the hilum has not been certainly excluded, though the evidence is against this supposition. In harmony with the mode of distribution of pneumococci it has been found that the initial lesions of lobar pneumonia are of the interstitial framework of the lung, with respect both to the grosser framework and to the alveolar framework. Hepatization begins centrally and spreads toward the periphery and is a constantly progressive process. With the development of hepatization the conspicuous interstitial lesions of the earliest stages gradually diminish and are often largely masked when complete lobar consolidation has developed. Resolution is frequently accompanied by a varying degree of organization of the grosser framework of the lung. A variable amount of organization of the alveolar exudate also may occur.

CONCLUSIONS.

1. In lobar pneumonia the pneumococcus primarily invades the lung tissue at some point or points near the root of the lobe.

2. The pneumococcus subsequently spreads throughout the lobe by way of the interstitial framework and lymphatic systems.

3. Lobar pneumonia, therefore, is primarily an interstitial infection of the lung.

4. Consolidation in lobar pneumonia begins in the alveolar tissue proximal to the hilum and progressively spreads to the more distal tissue until complete lobar consolidation develops.

EXPLANATION OF PLATES.

PLATE 22.

FIG. 1. Monkey 83. Lobar pneumonia, Pneumococcus Type I; died on 8th day. Posterior aspect of lungs showing lobar consolidation of right middle and lower lobes, partial consolidation of right upper lobe, and normal left lung.

PLATE 23.

FIG. 2. Monkey 83. Lobar pneumonia, Pneumococcus Type I; died on 8th day. Cut surface of lungs showing red and gray hepatization of right upper and lower lobes, gray hepatization of right middle lobe, and normal left lung.

PLATE 24.

FIG. 3. Monkey 86. Lobar pneumonia, Pneumococcus Type I; died on 14th day. Cut surface of lungs showing gray hepatization of both lower lobes.

FIG. 4. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Section from right lower lobe showing thickening of vascular adventitia and of bronchial walls. × 3.5.

PLATE 25.

FIGS. 5 and 6. Monkey 88. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Sections from left lower lobe and right lower lobe, respectively, showing involvement of interstitial framework of lung. × 3.5.

PLATE 26.

FIG. 7. Monkey 112. Lobar pneumonia, Pneumococcus Type I; died on 6th day; stage of engorgement and red and gray hepatization. Section from left lower lobe showing beginning peribronchial consolidation. × 3.5.

FIG. 8. Monkey 29. Lobar pneumonia, Pneumococcus Type I; died on 2nd day; stage of engorgement and red hepatization. Section through left lower lobe showing consolidation of central portion with engorgement and edema of peripheral portions.

PLATE 27.

FIG. 9. Monkey 93. Lobar pneumonia, Pneumococcus Type I; died on 13th day; stage of gray hepatization. Section through right lower lobe showing uniform consolidation except at anterior margin. × 3.5.

FIG. 10. Monkey 107. Abortive lobar pneumonia, Pneumococcus Type III; recovered by lysis on 4th day; killed on 5th day. Section through right lower lobe showing limitation of involvement to interstitial framework of lung. × 3.5.

PLATE 28.

FIG. 11. Monkey 17. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Edema and leucocytic infiltration of adventitia of large pulmonary vein. × 100.

PLATE 29.

FIG. 12. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Edema and leucocytic infiltration of wall of large bronchus. × 100.

FIG. 13. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Perivascular edema and leucocytic infiltration of a small peripheral vein. × 100.

PLATE 30.

FIG. 14. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Leucocytic infiltration about a small vein. × 400.

PLATE 31.

FIG. 15. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Bronchiole and pulmonary arteries showing leucocytic infiltration of walls with absence of exudate in bronchiole and adjacent alveoli. × 100.

FIG. 16. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Edema and leucocytic infiltration of interlobular septum. Lymphatics filled with polymorphonuclear leucocytes. × 100.

PLATE 32.

FIG. 17. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Distended lymphatic filled with polymorphonuclear leucocytes.

FIG. 18. Monkey 98. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Capillary engorgement and atelectasis of alveoli. × 400.

PLATE 33.

FIG. 19. Monkey 72. Killed 3 hours after intratracheal injection of Pneumococcus Type I. Invasion of wall of large bronchus by pneumococci.

PLATE 34.

FIG. 20. Monkey 88. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Pneumococci in wall of large bronchus, right lower lobe. × 1,000.

FIG. 21. Monkey 88. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement. Pneumococci in perivascular tissue of small pulmonary vein near periphery. × 1,000.

PLATE 35.

FIG. 22. Monkey 72. Killed 3 hours after intratracheal injection of Pneumococcus Type I. Early alveolar lesion showing polymorphonuclear leucocytic infiltration of walls of alveolar duct and adjacent alveoli with absence of exudate in duct and alveoli. × 100.

PLATE 36.

FIG. 23. Monkey 5. Lobar pneumonia, Pneumococcus Type I; died on 1st day; stage of engorgement and red hepatization. Leucocytic infiltration of alveolar walls beyond the margin of the consolidated area; also distention of perivascular lymphatics. × 100.

PLATE 37.

FIG. 24. Monkey 6. Lobar pneumonia, Pneumococcus Type I; died on 4th day; stage of engorgement and red hepatization. Section from periphery of right lower lobe showing pneumococci in alveolar walls.

PLATE 38.

FIG. 25. Monkey 23. Lobar pneumonia, Pneumococcus Type I; died on 5th day; stage of red hepatization. Margin of consolidated area showing alveoli containing varying proportions of serum, red blood corpuscles, fibrin, polymorphonuclear leucocytes, and large mononuclear cells. × 100.

PLATE 39.

FIG. 26. Monkey 23. Lobar pneumonia, Pneumococcus Type I; died on 5th day; stage of red hepatization. Section from margin of consolidated area showing pneumococci in alveolar walls and in serous exudate in alveoli.

PLATE 40.

FIG. 27. Monkey 110. Lobar pneumonia, Pneumococcus Type I; died on 7th day; stage of red and gray hepatization. Alveolar exudate of coagulated serum, fibrin, polymorphonuclear leucocytes, and large mononuclear cells. × 400.

PLATE 41.

FIG. 28. Monkey 112. Lobar pneumonia, Pneumococcus Type I; died on 6th day; stage of red and gray hepatization. Alveolar consolidation. × 100.

FIG. 29. Monkey 26. Lobar pneumonia, Pneumococcus Type I; killed on 9th day; stage of gray hepatization. Alveoli filled with exudate of polymorphonuclear leucocytes. × 100.

PLATE 42.

FIG. 30. Monkey 89. Lobar pneumonia, Pneumococcus Type I; killed 4 days after recovery by crisis. Resolution of alveolar exudate. × 100.

FIG. 31. Monkey 64. Lobar pneumonia, Pneumococcus Type I; killed on 30th day. Organization and resolution. × 100.

PLATE 43.

FIG. 32. Monkey 14. Lobar pneumonia, Pneumococcus Type I; died on 17th day. Organization. × 100.

FIG. 33. Monkey 23. Lobar pneumonia, Pneumococcus Type I; died on 5th day. Marginal sinus of bronchial lymph node filled with large mononuclear phagocytes, polymorphonuclear leucocytes, and lymphocytes. × 400.

PLATE 44.

FIG. 34. Monkey 23. Lobar pneumonia, Pneumococcus Type I; died on 5th day. Bone marrow of femur showing almost complete exhaustion of hematopoietic cells. × 400.

FIG. 35. Monkey 26. Lobar pneumonia, Pneumococcus Type I; killed on 9th day. Bone marrow of femur showing hyperplasia. × 400.

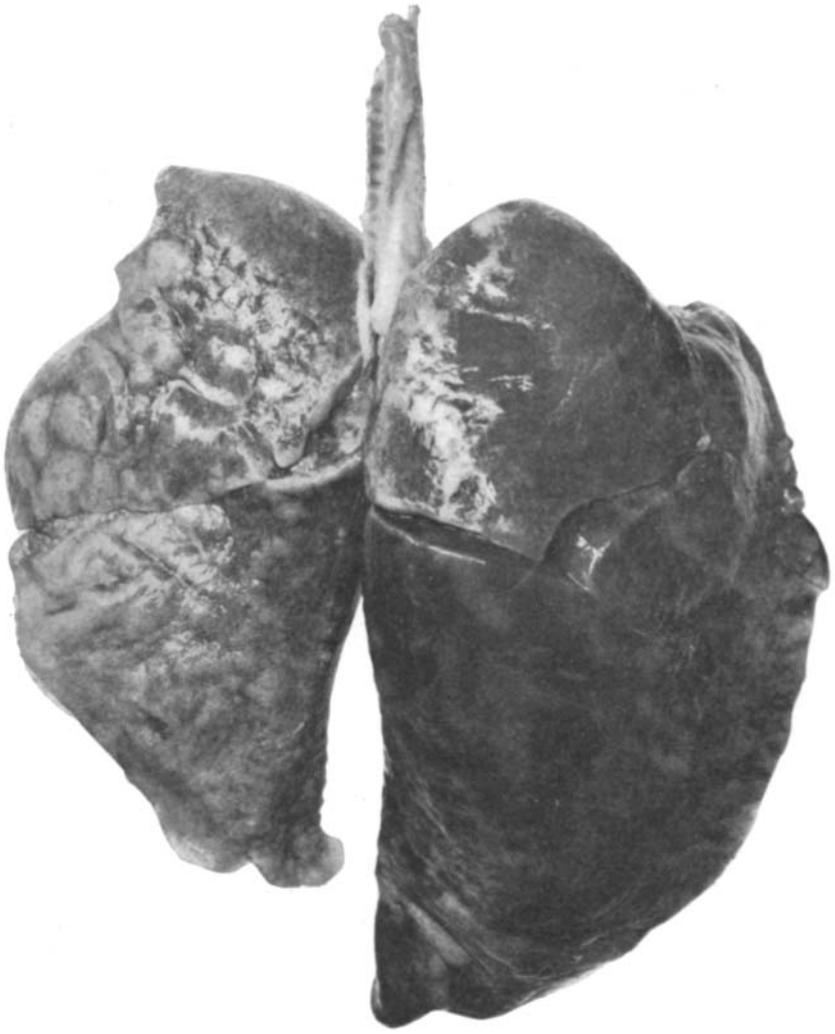

FIG. 1.

(Blake and Cecil: Experimental pneumonia. II.)

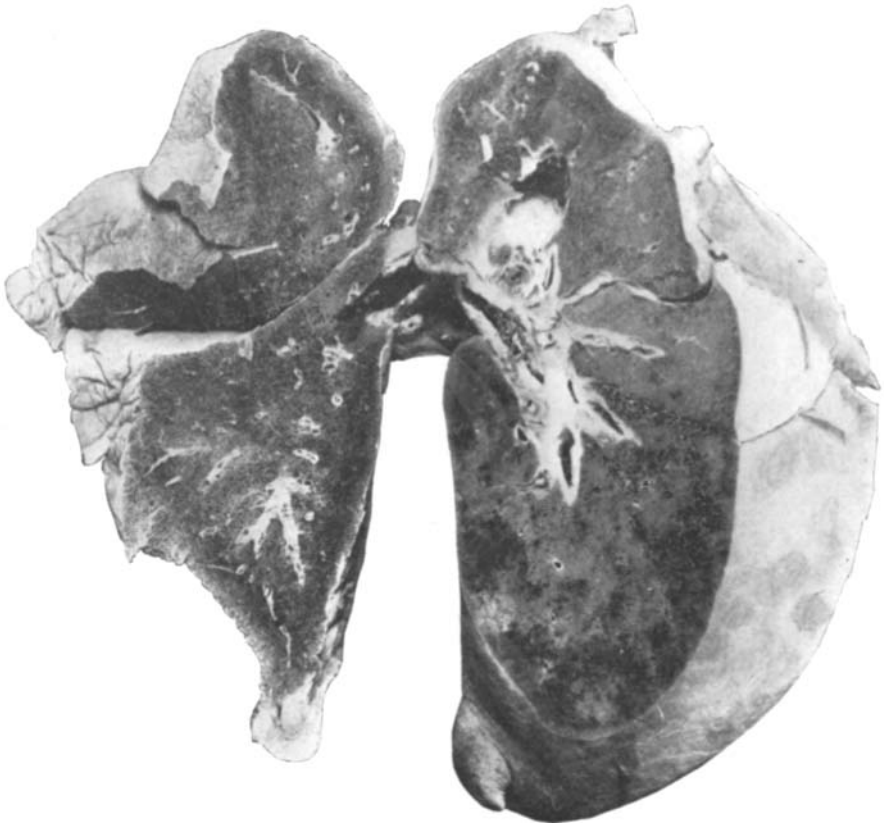

FIG. 2.

(Blake and Cecil: Experimental pneumonia. II.)

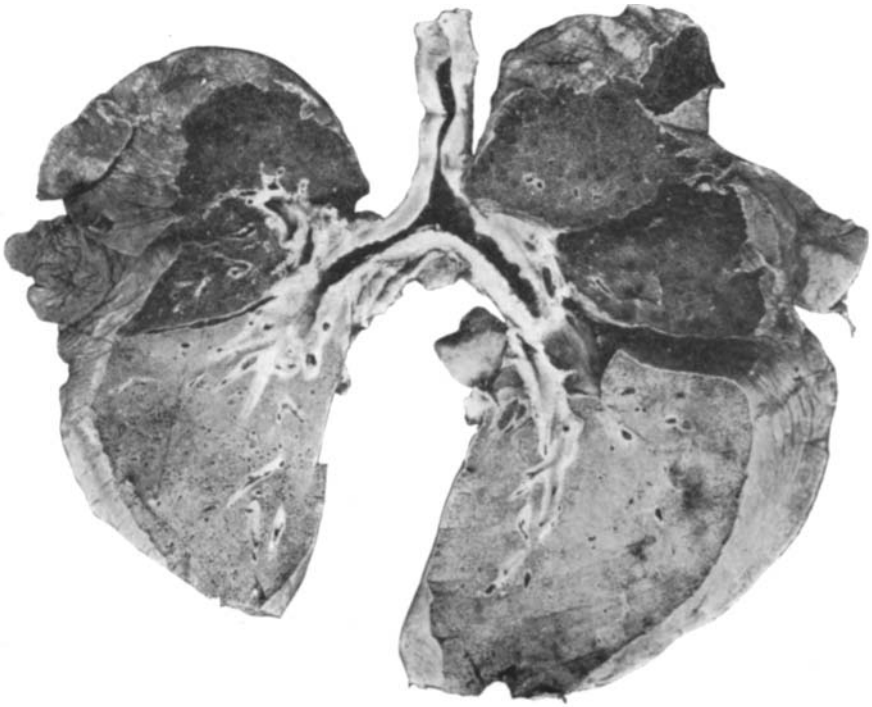

FIG. 3.

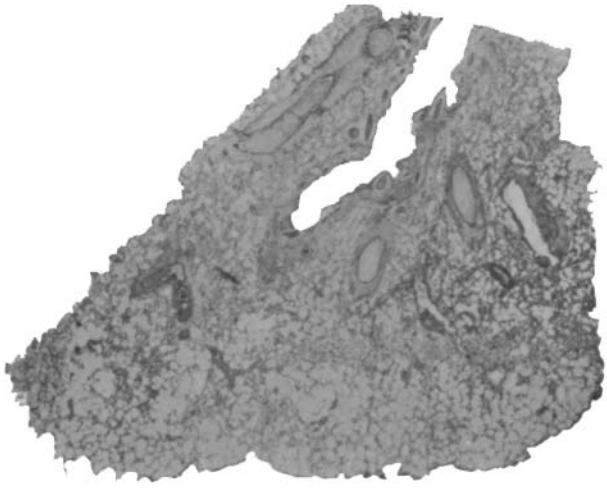

FIG. 4.

(Blake and Cecil: Experimental pneumonia. II.)

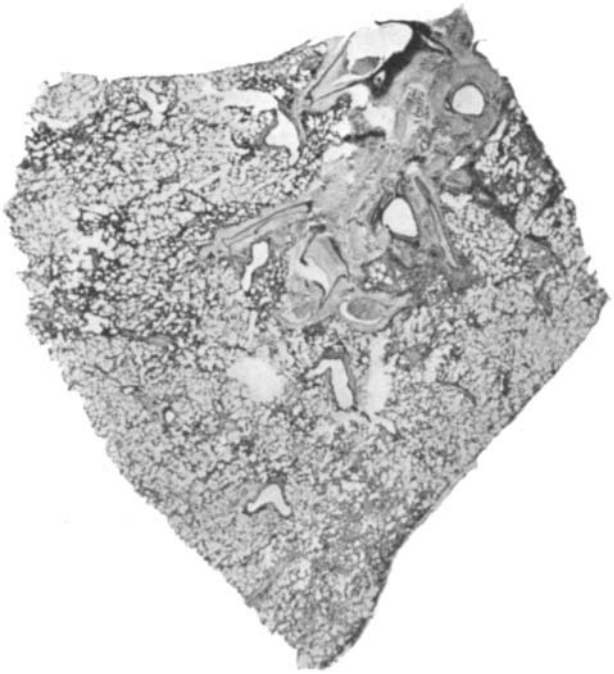

FIG. 5.

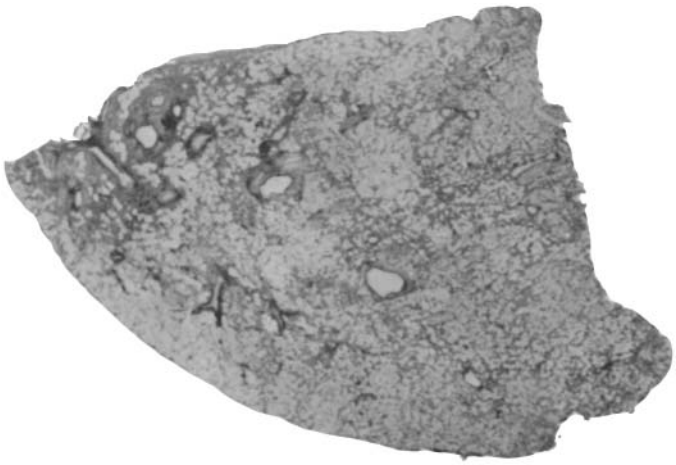

FIG. 6.

(Blake and Cecil: Experimental pneumonia. II.)

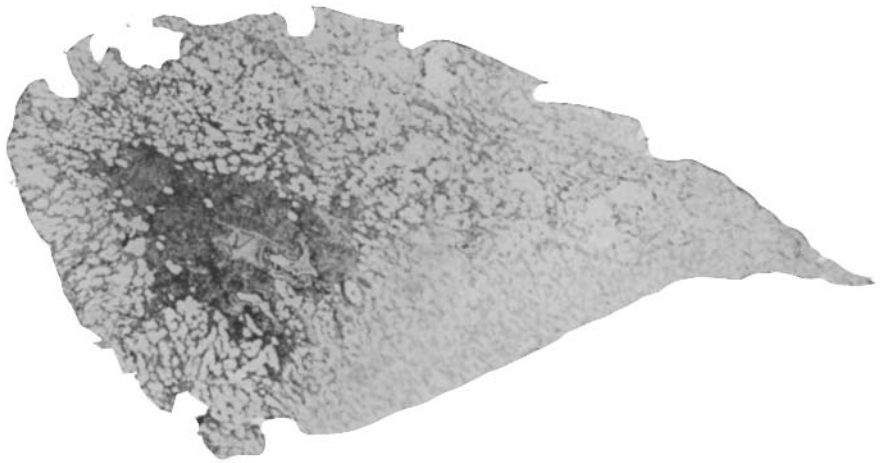

FIG. 7.

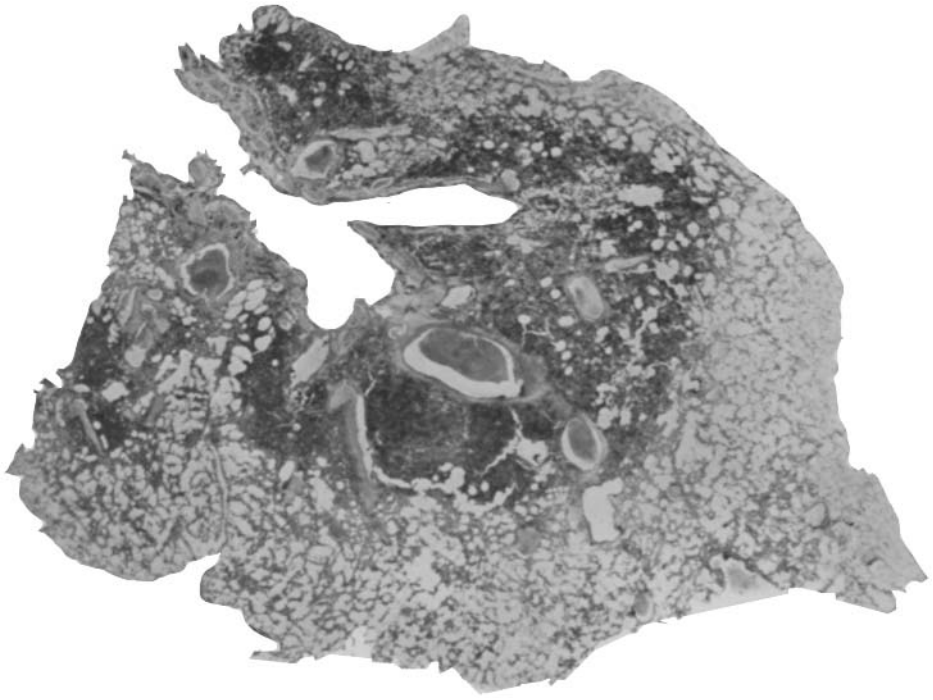

FIG. 8.

(Blake and Cecil: Experimental pneumonia. II.)

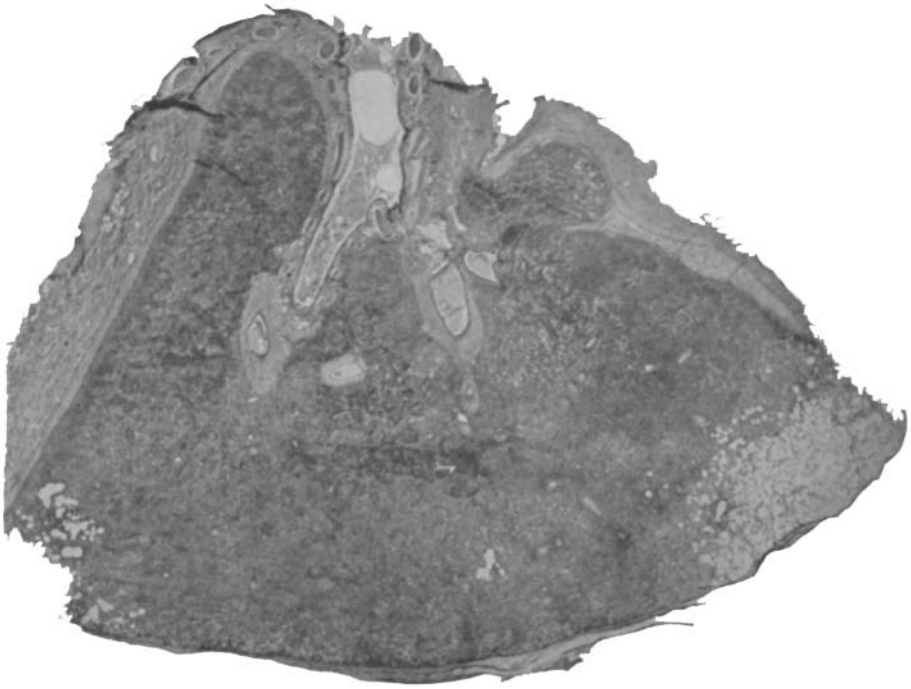

FIG. 9.

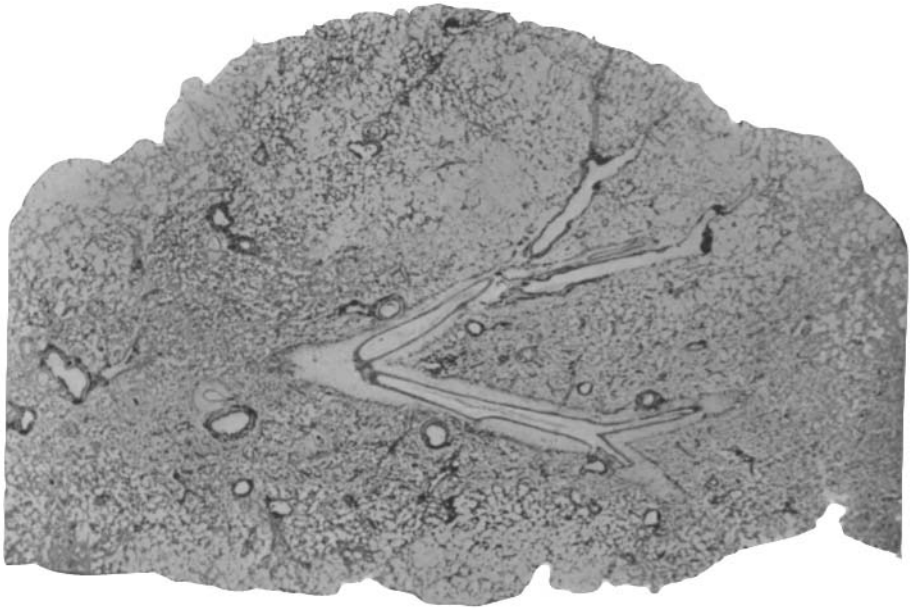

FIG. 10.

(Blake and Cecil: Experimental pneumonia. II.)

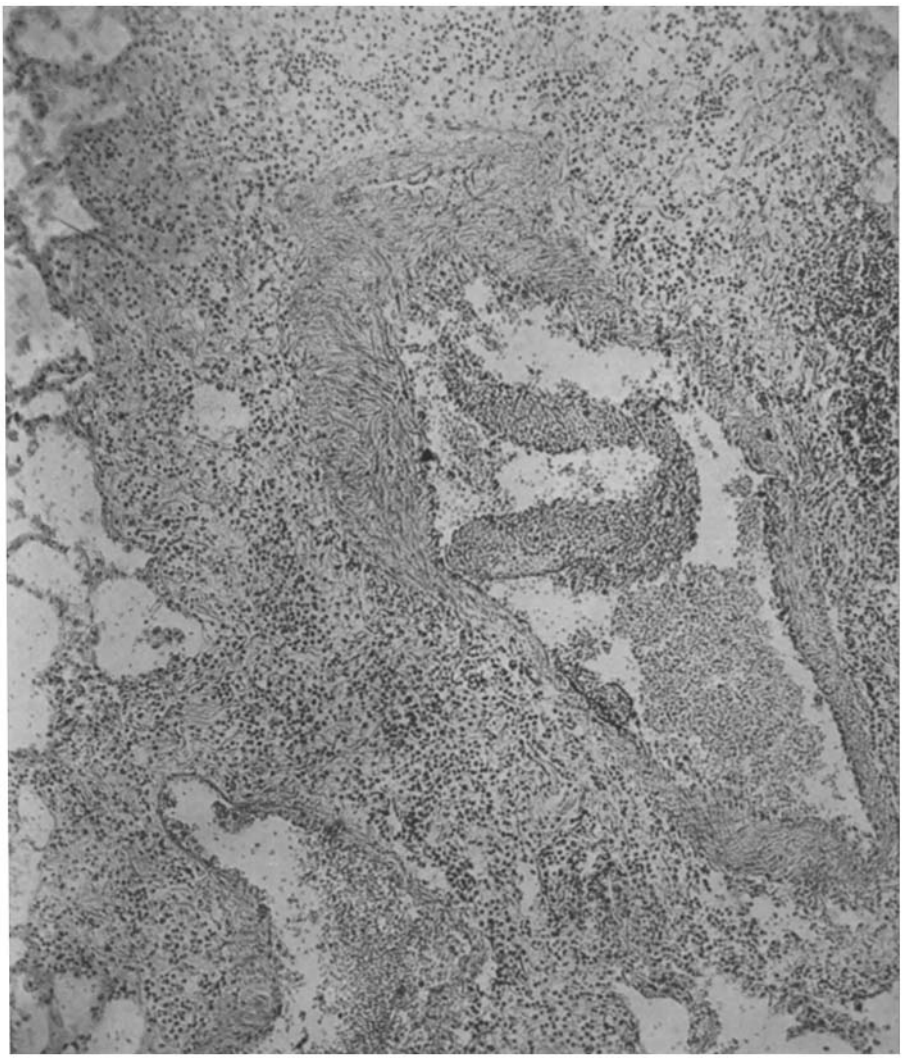

FIG. 11.

(Blake and Cecil: Experimental pneumonia. II.)

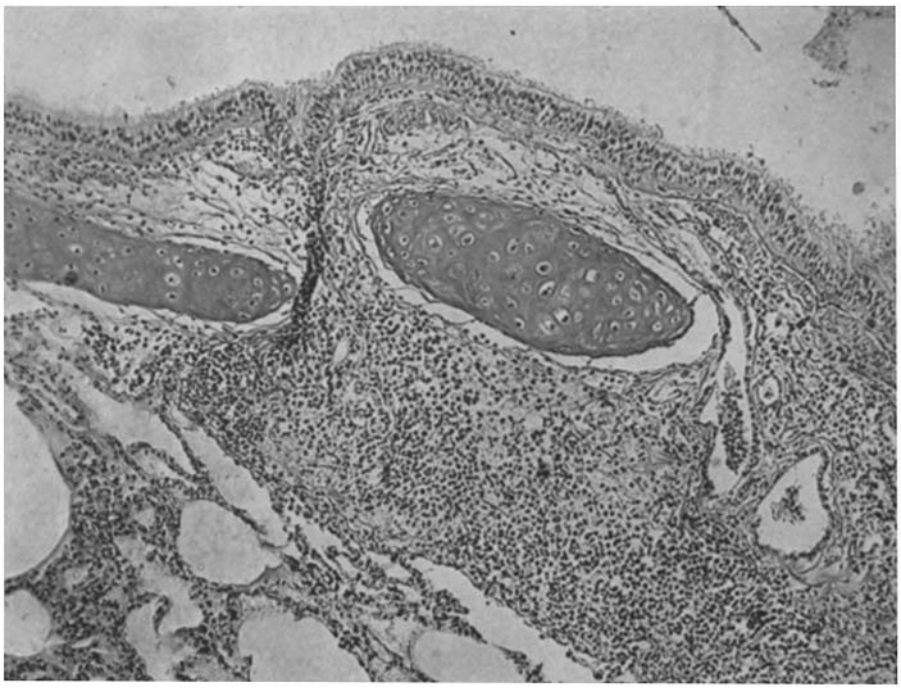

FIG. 12.

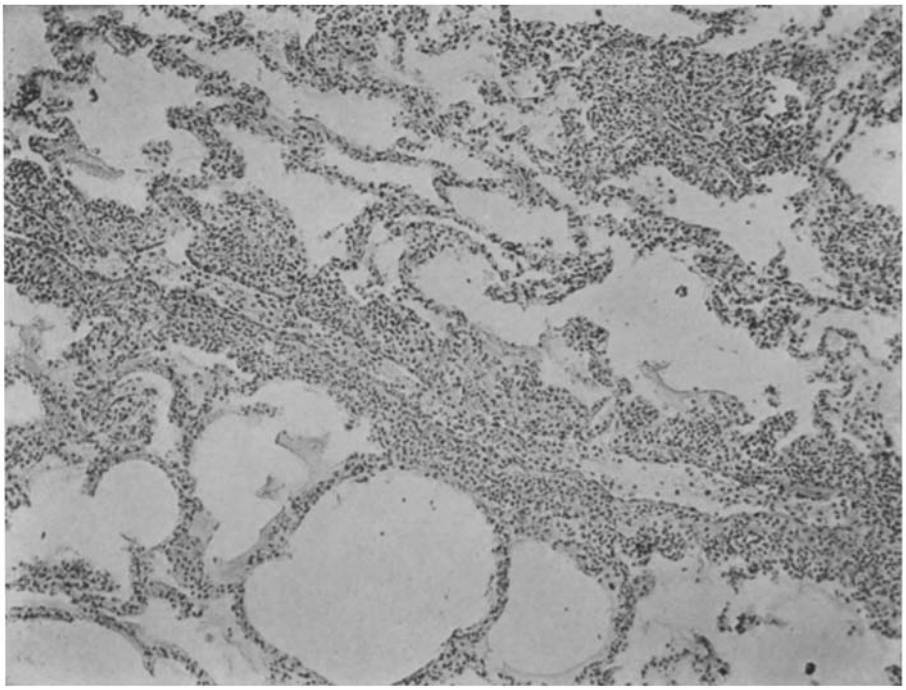

FIG. 13.

(Blake and Cecil: Experimental pneumonia. II.)

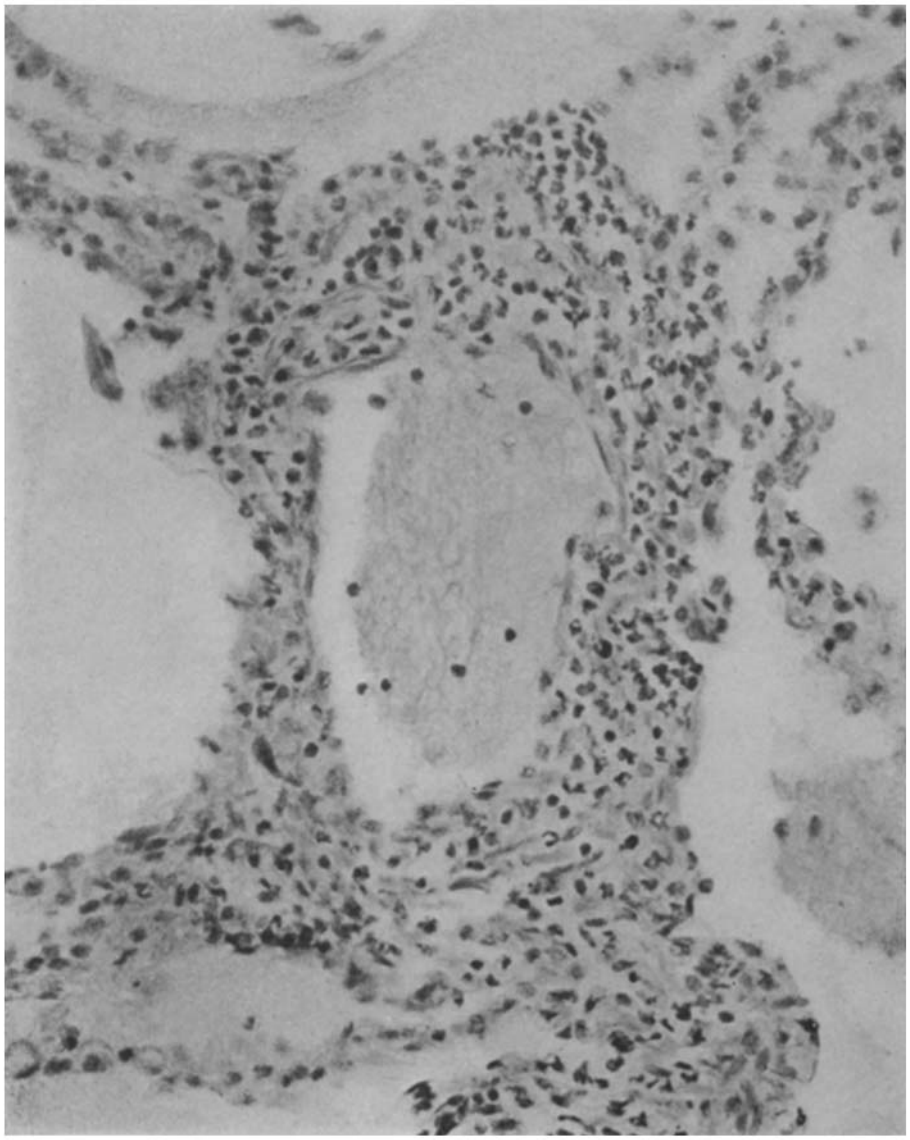

FIG. 14.

(Blake and Cecil: Experimental pneumonia. II.)

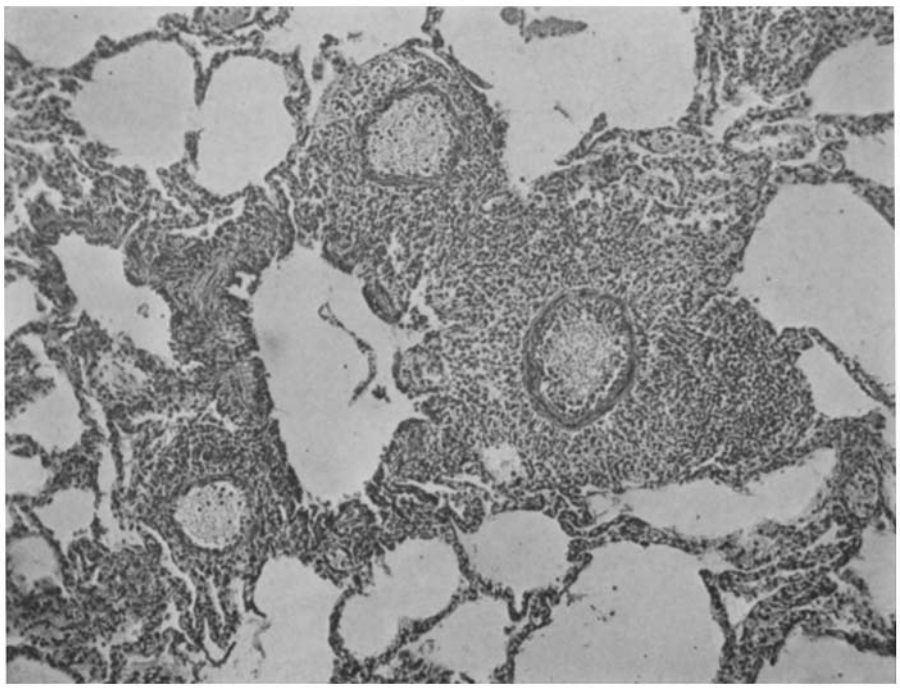

FIG. 15.

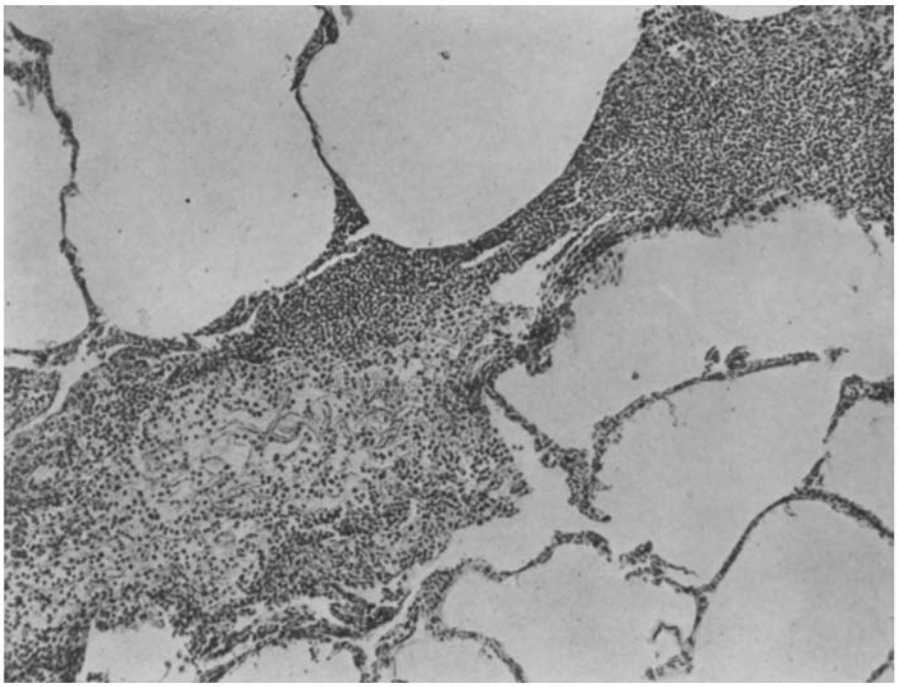

FIG. 16.

(Blake and Cecil: Experimental pneumonia. II.)

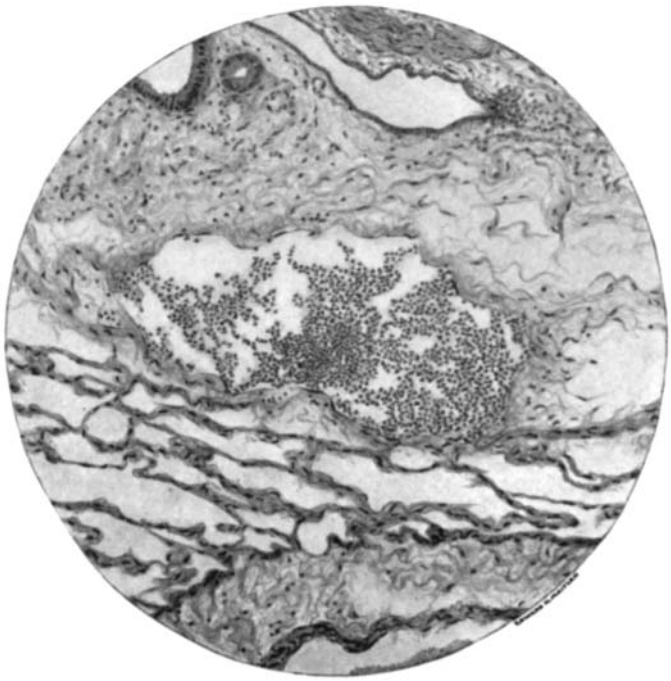

FIG. 17.

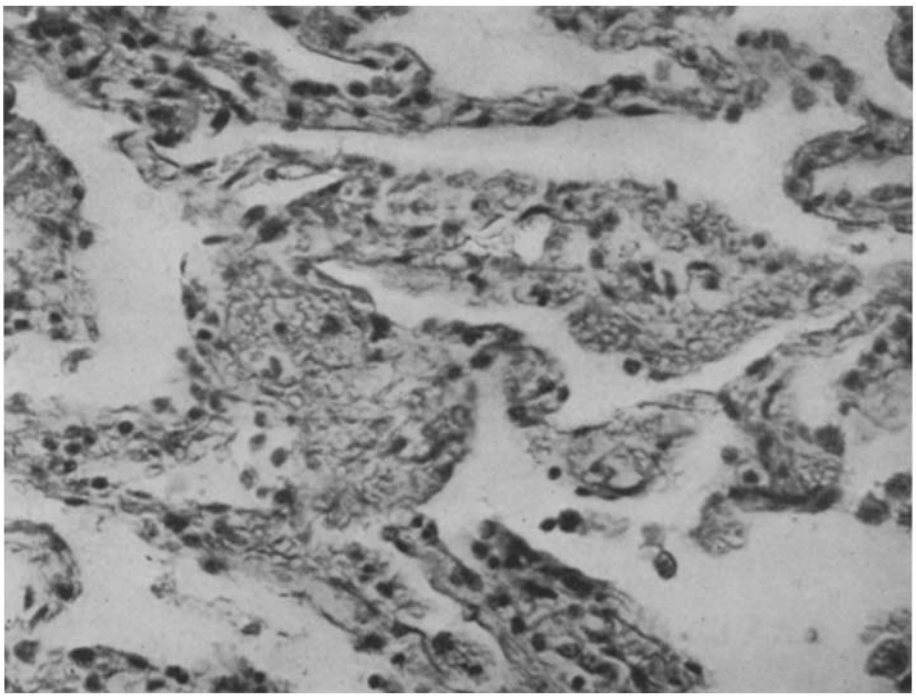

FIG. 18.

(Blake and Cecil: Experimental pneumonia. II.)

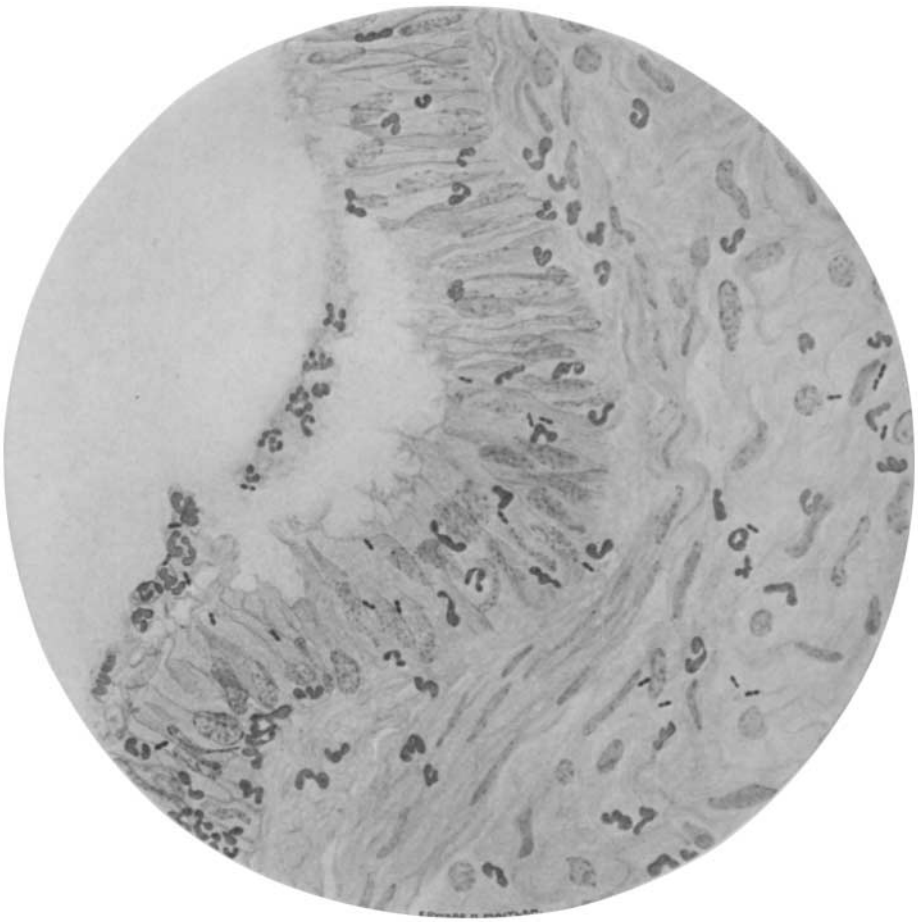

FIG. 19.

(Blake and Cecil: Experimental pneumonia. II.)

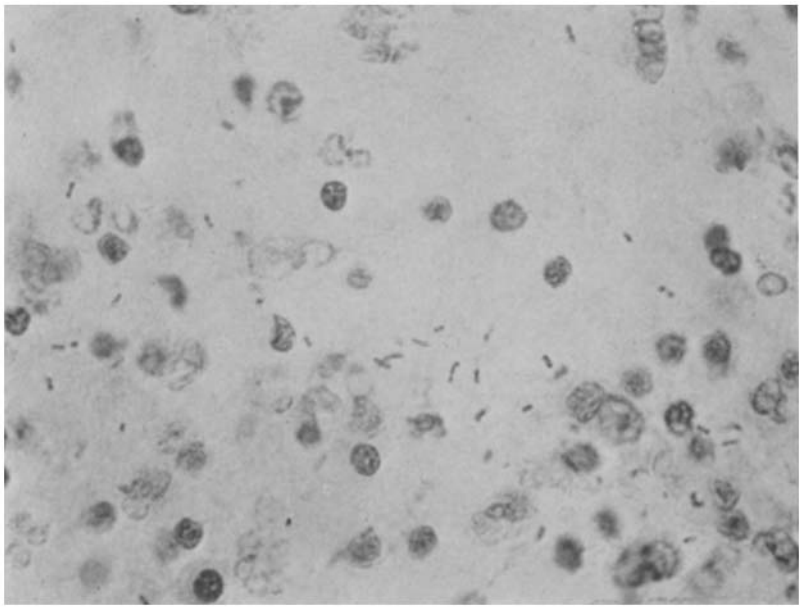

FIG. 20.

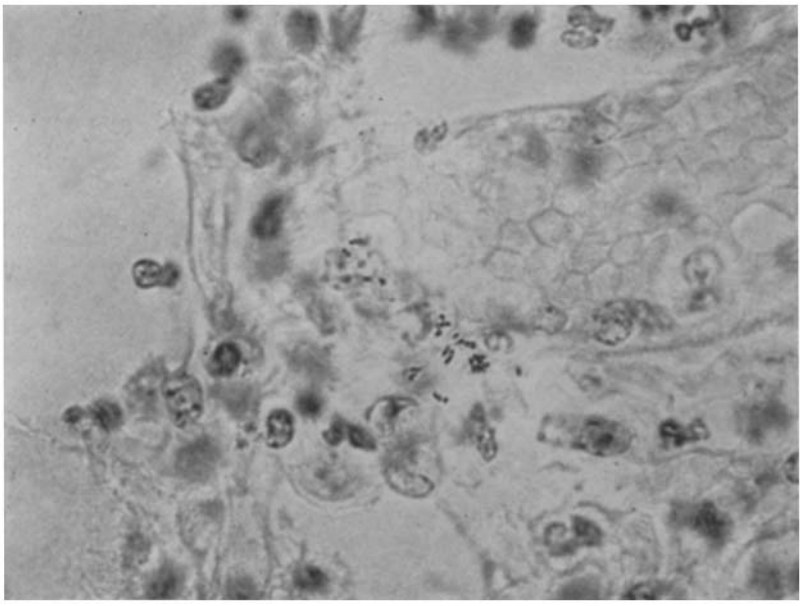

FIG. 21.

(Blake and Cecil: Experimental pneumonia. II.)

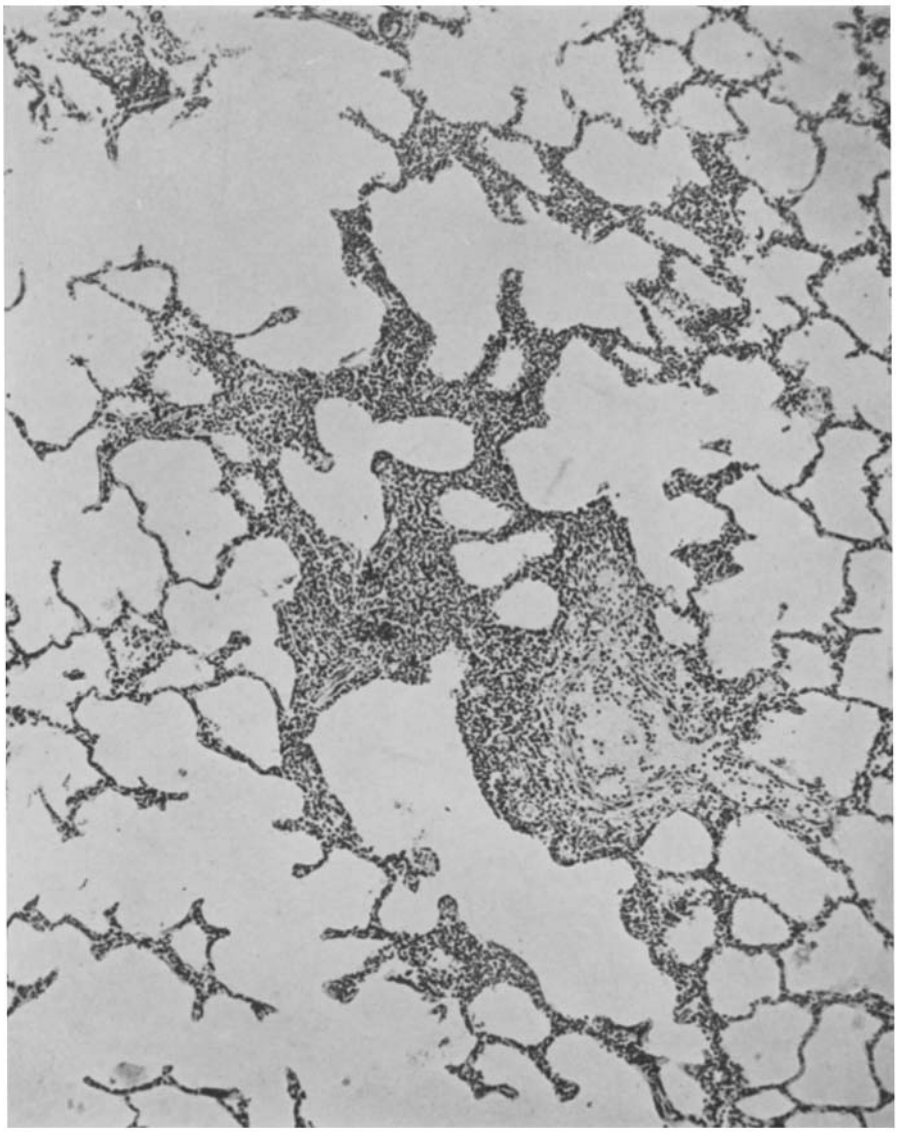

FIG. 22.

(Blake and Cecil: Experimental pneumonia. II.)

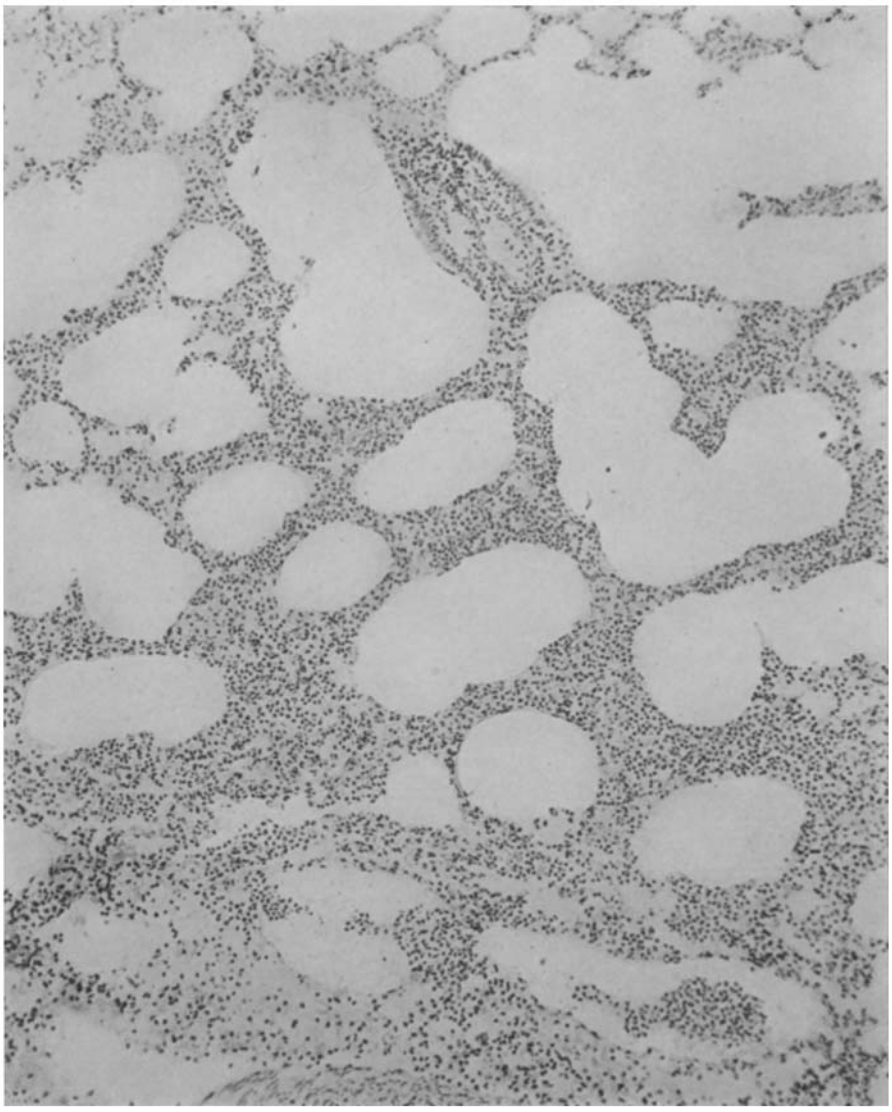

FIG. 23.

(Blake and Cecil: Experimental pneumonia. II.)

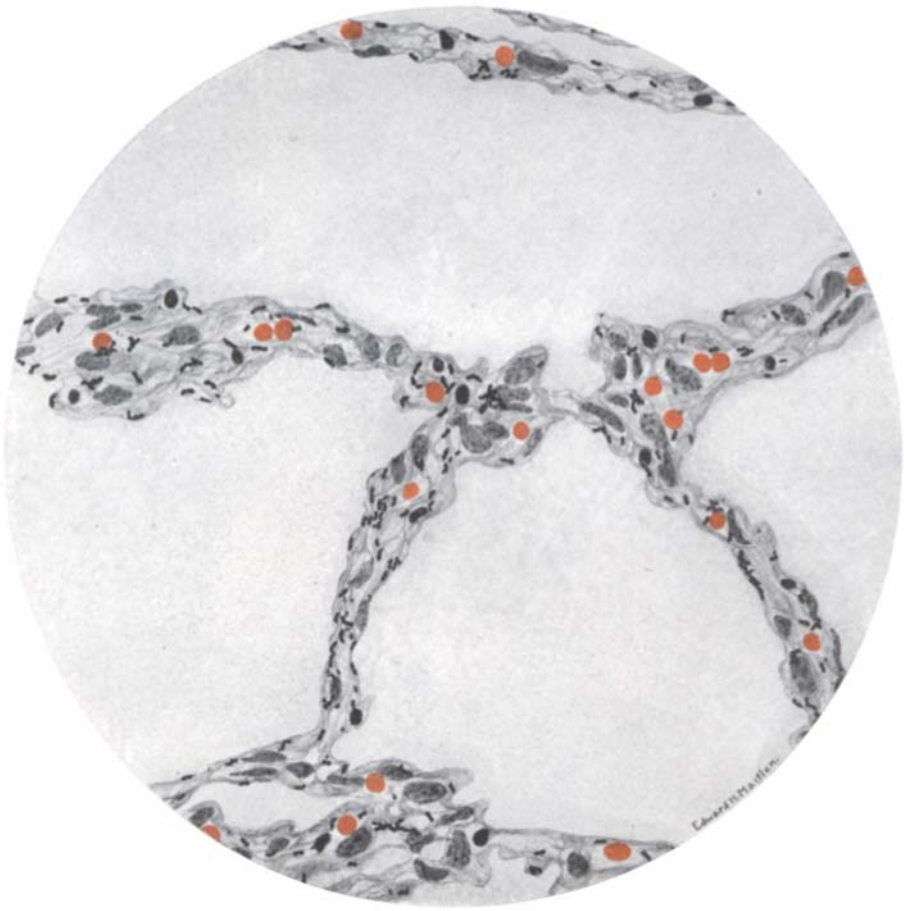

FIG. 24.

(Blake and Cecil: Experimental pneumonia. II.)

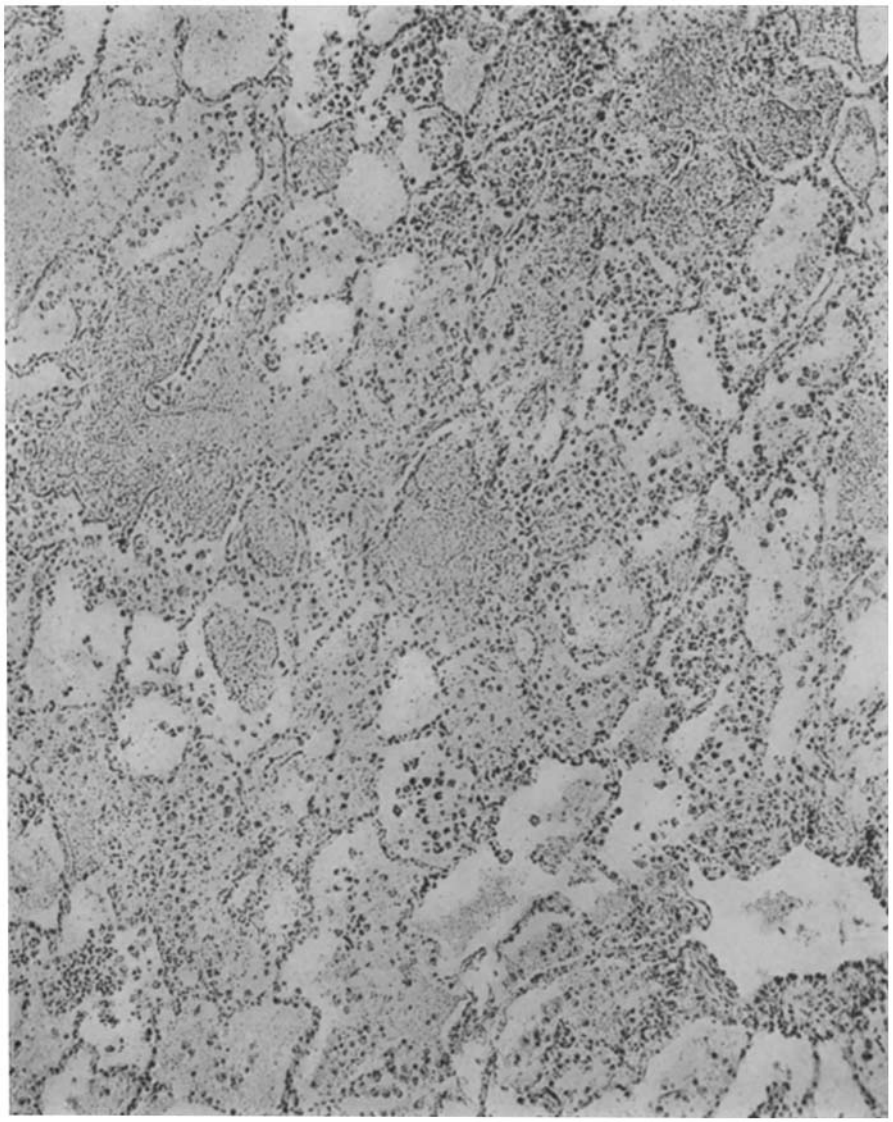

FIG. 25.

(Blake and Cecil: Experimental pneumonia. II.)

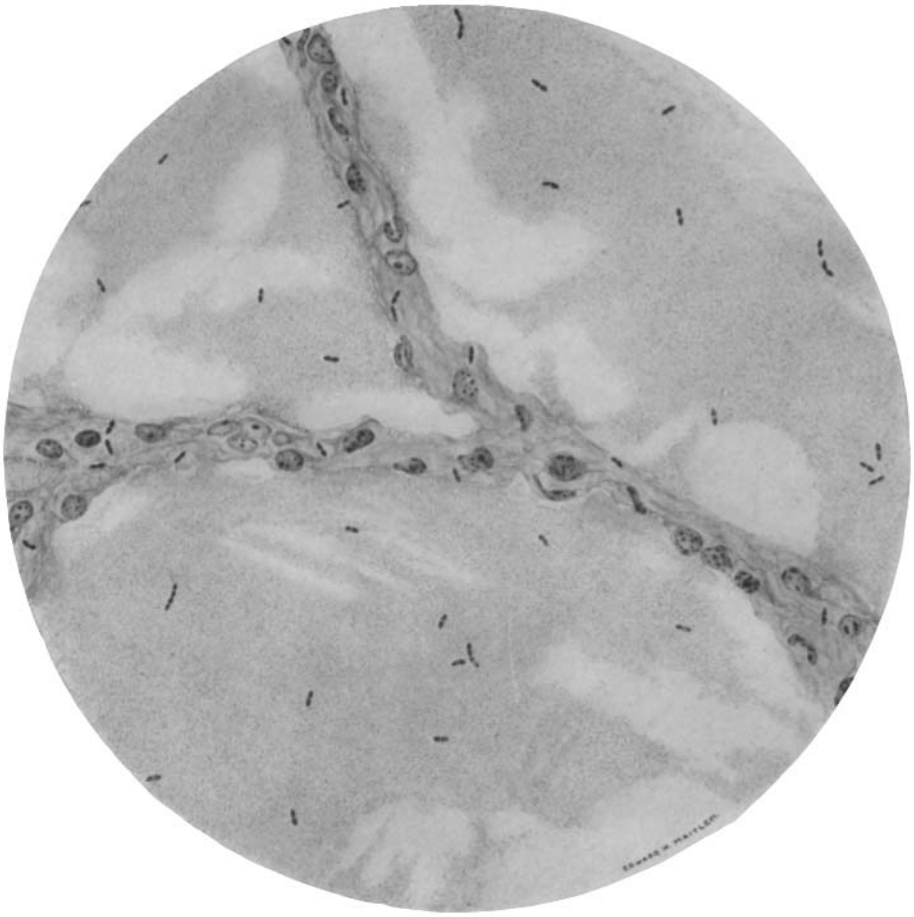

FIG. 26

(Blake and Cecil: Experimental pneumonia. II.)

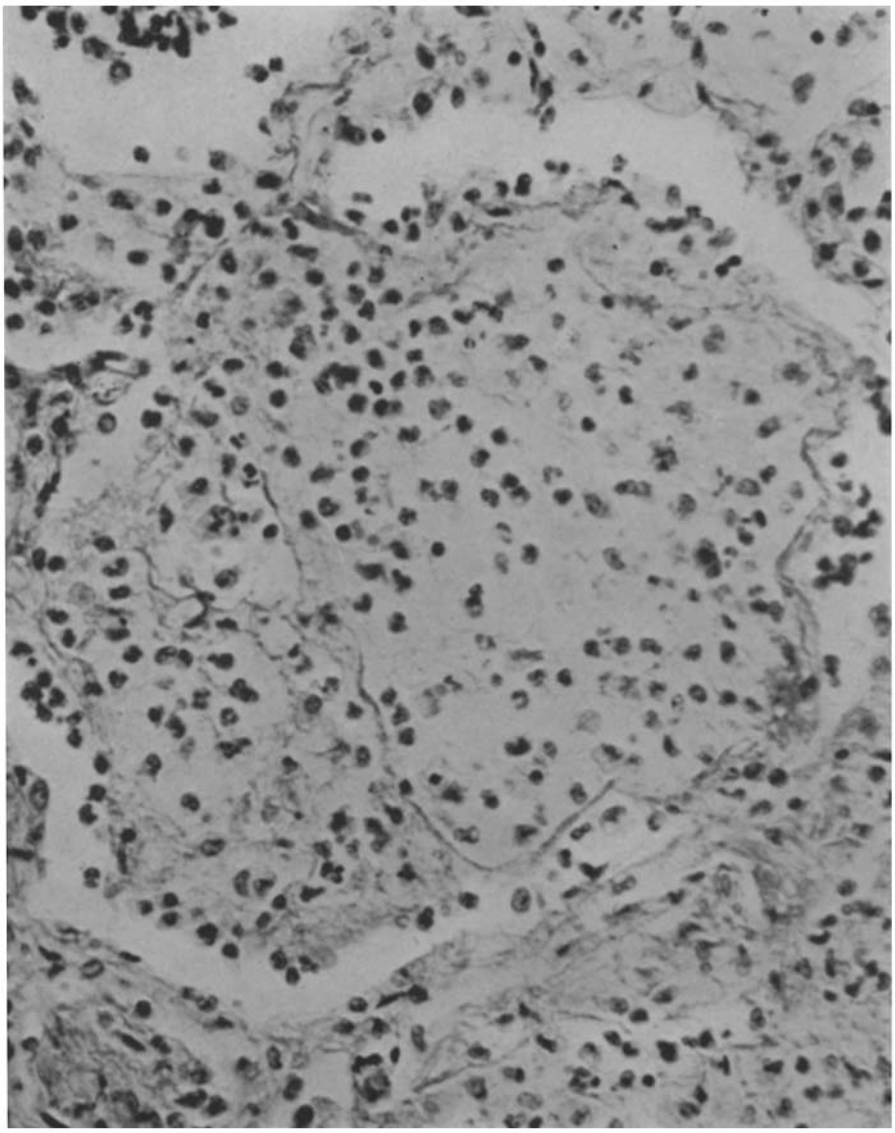

FIG. 27.

(Blake and Cecil: Experimental pneumonia. II.)

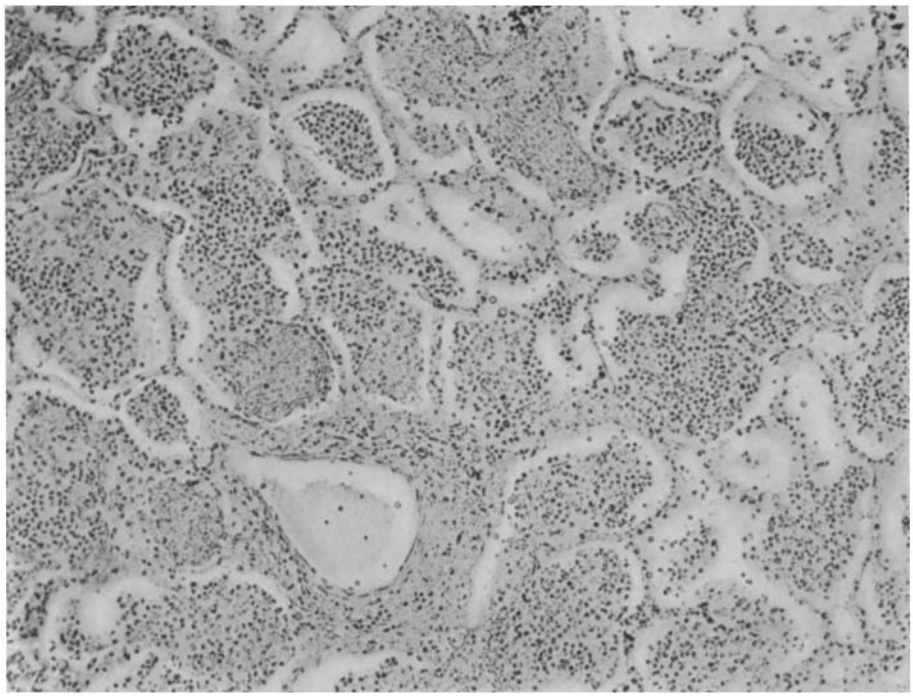

FIG. 28.

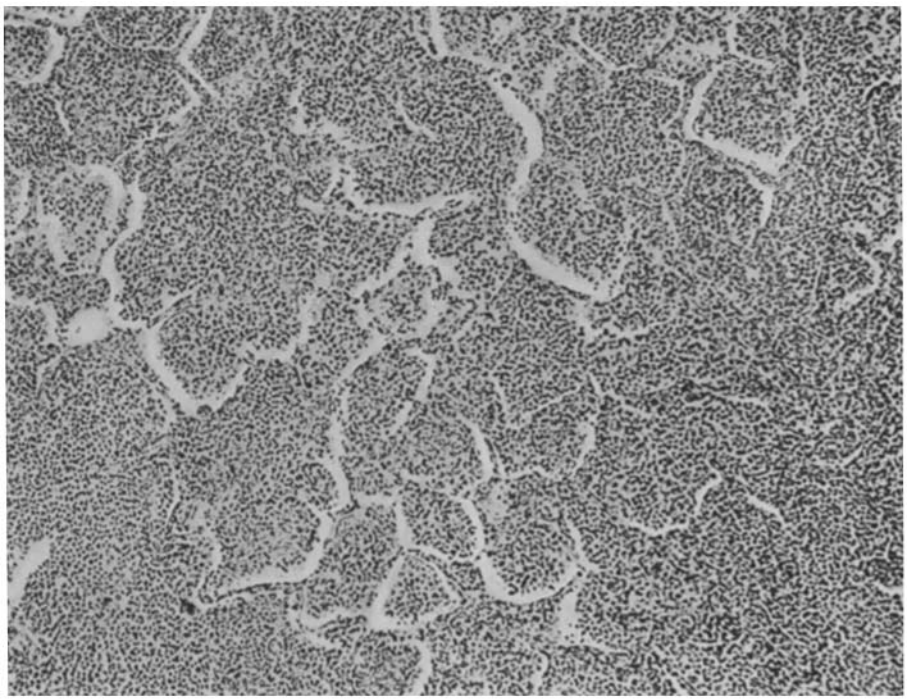

FIG. 29.

(Blake and Cecil: Experimental pneumonia. II.)

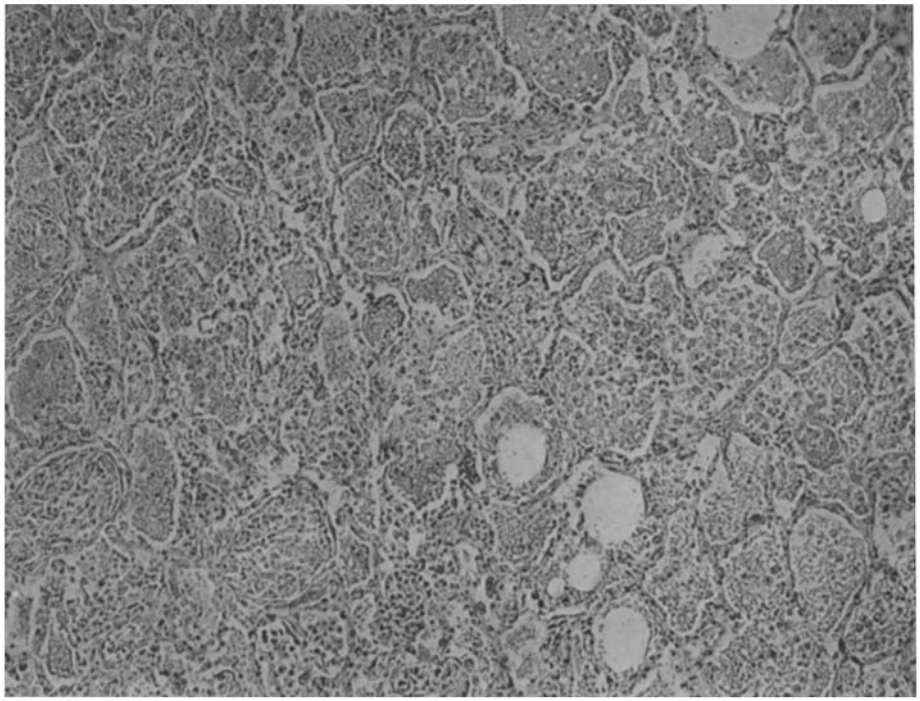

FIG. 30

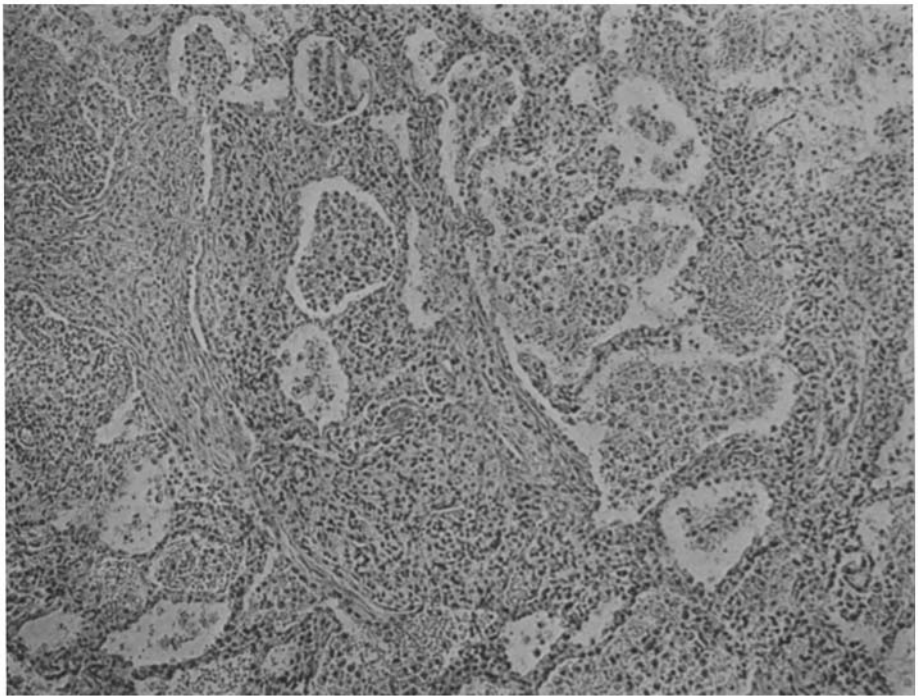

FIG. 31

(Blake and Cecil: Experimental pneumonia. II.)

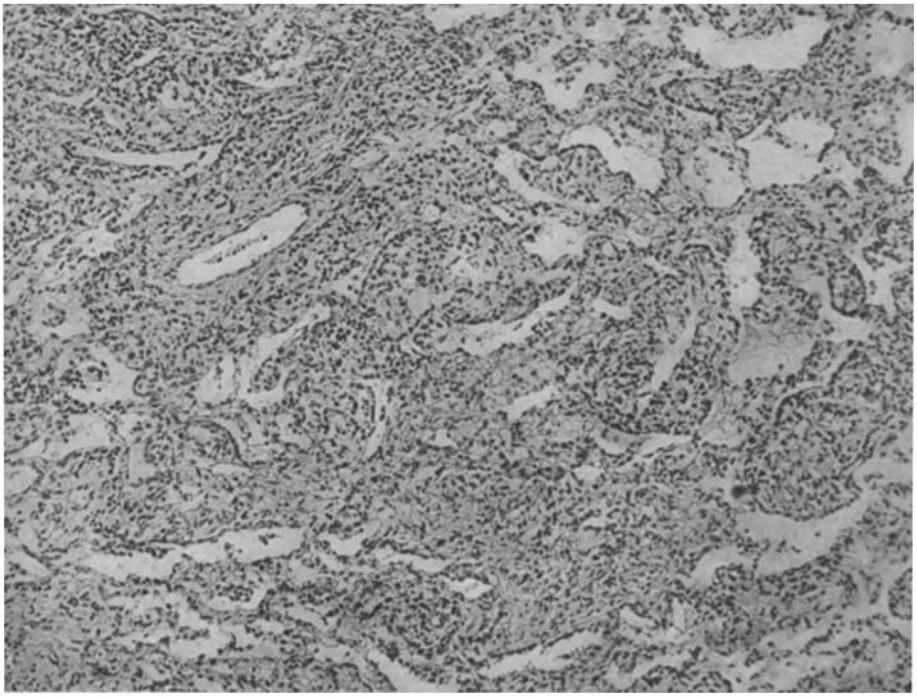

FIG. 32.

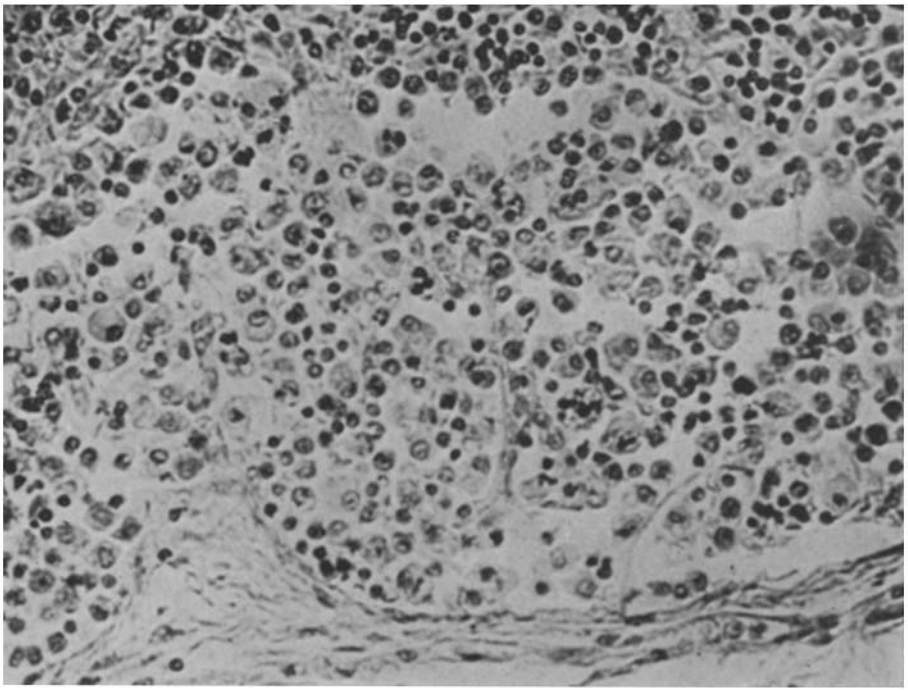

FIG. 33.

(Blake and Cecil: Experimental pneumonia. II.)

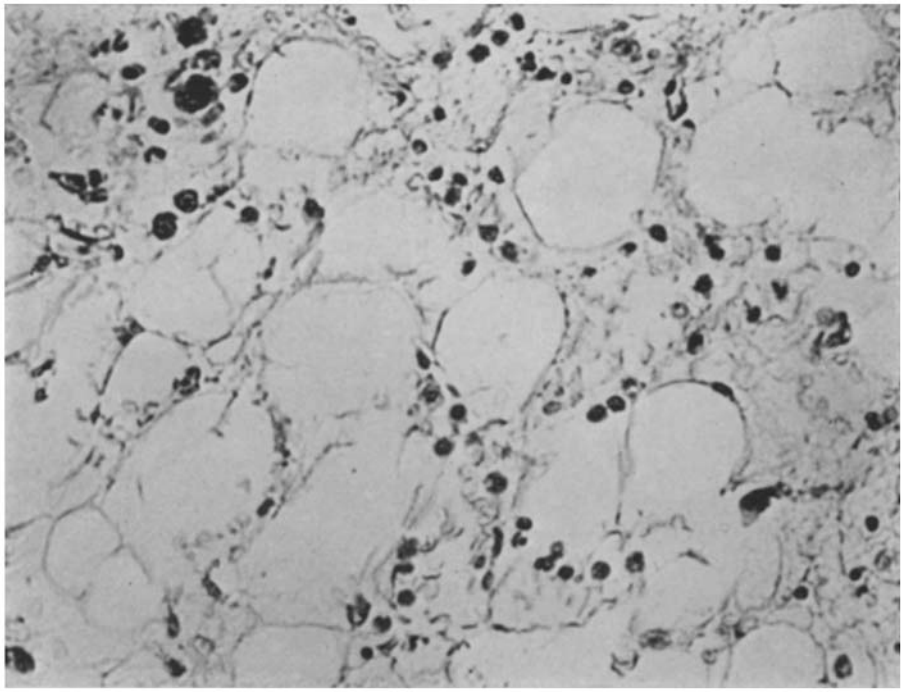

FIG. 34.

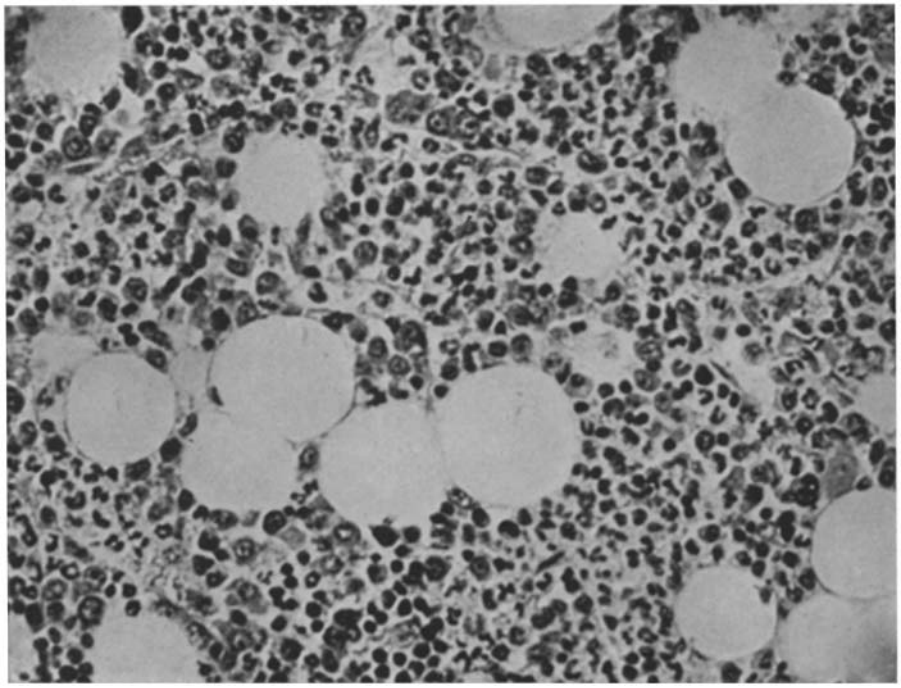

FIG. 35.

(Blake and Cecil: Experimental pneumonia. II.)