EXPERIMENTAL STUDY OF ORGANIZATION IN LOBAR PNEUMONIA.

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PLATES 17 TO 19.

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Healing of injured and intensely inflamed vascular tissues is characterized by the formation of granulation tissue. A striking exception to this is the perfect healing of the lung in most cases of lobar pneumonia. Here, complete resolution with removal of the exudate and regeneration of the injured lung result. Occasionally, however, the exudate persists, and, as elsewhere, it is dealt with by an ingrowth of capillaries and connective tissue cells.

The factors determining the result in the inflamed lung are little understood and the explanations offered for the occurrence of unresolved lobar pneumonia are as inconclusive as those for the perfect healing of the lung. Ziegler (1) suggested that the retention of the exudate and its organization in unresolved lobar pneumonia probably depended upon recurring exudates, eventually requiring organization for their removal. Von Kahlden (2) considered an excessive formation and retention of fibrin the probable cause. Kohn (3) believed that organization of the exudate occurred as a result of irritation of the interlobular and pleural connective tissue. Köster (4) thought that blocking of the lymph channels in the involved area was responsible. Marchand (5) considered alcoholism a predisposing factor, and Heschl (6) reported its greater frequency in emaciated individuals. Amburger (7) advocated syphilis as the cause. Another conception was that of Corrigan (8) who described it as a special disease analogous to cirrhosis of the liver.

In 1903 Flexner (9) found that consolidated lung in the stage of red hepatization autolyzed imperfectly, whereas in the stage of gray hepatization it autolyzed rapidly and perfectly. He concluded that in unresolved pneumonia because of some disproportion between the leukocytes and other constituents, or other cause unknown, the inflammatory exudate failed to autolyze perfectly, could not be absorbed, and hence underwent organization.

A few years later Opie (10) in the course of a study of leukocytic enzymes noted that when a mixture of dog serum, leukocytes, and fibrin were incubated, autolysis of the leukocytes and digestion of the fibrin were inhibited, whereas when no serum was present, the leukocytes autolyzed readily and the fibrin was completely digested.

In 1914, in association with Winternitz (11), a study of the circulation in the pneumonic lung was made. It was observed that in the later stages of lobar pneumonia, the circulation through the consolidated portion is extremely poor. This was strikingly shown in animals stained with trypan blue. Two sets of experiments were undertaken. In one series, rabbits were injected intravenously with trypan blue, and, following the injection of the dye, the animals were given an intrabronchial injection of pneumococci. The trypan blue was again introduced intravenously during the progress of the pneumonia. In the other series of animals, the first procedure was the injection of pneumococci intrabronchially, and 40 or more hours later the intravenous injections of trypan blue were begun. In the animals receiving trypan blue first, and during the course of the pneumonia, the consolidated portions of the lung at autopsy were intensely blue, whereas in those animals in which the trypan blue was injected only in the later stages of the pneumonia, it was found that but very little of the dye penetrated the consolidated portions. It was inferred that little or no serum reaches the exudate in the alveoli in the stage of gray hepatization, and it was suggested that if this were true, autolysis of the leukocytes and digestion of fibrin in the lung in the late stages of pneumonia are not inhibited and resolution therefore occurs.

Not only do the experiments mentioned above suggest that the absence of the serum from the exudate may be a determining factor in bringing about resolution, but they likewise suggest that the persistence of the exudate in unresolved pneumonia may depend upon the presence in the exudate of sufficient serum to prevent the autolysis of the leukocytes and digestion of the fibrin. If this is true, persistence of the exudate and its organization, in lobar pneumonia, might be expected to develop in those cases in which the circulation in the lung, in the later stages of the process, was good enough to permit a considerable amount of serum to reach the exudate in the alveoli.

The experiments to be reported in this paper were undertaken to determine the significance of the presence of serum in the exudate, in the late stages of pneumonia. The method of injecting the serum depended upon an observation made in the study mentioned above (11). It was found that although very little of the trypan blue,

when injected intravenously, penetrated the lung in the later stage of pneumonia, the exudate offered no barrier to its penetration when it was injected intrabronchially.

The experiments were carried out in dogs because of this animal's resistance to the pneumococcus. Twenty-five animals in all were injected. In nineteen lobar pneumonia was produced with a Group I pneumococcus, according to the technique of Lamar and Meltzer (12). In each case, before the injection of the pneumococci, an x-ray was taken to show the position of the catheter. Seven of the animals were kept as controls, without further treatment. In the other twelve, sterile dog blood serum was injected into the same lobe that received the pneumococci once a day for 4 to 7 days, beginning 48 to 72 hours after the intrabronchial injection of pneumococci. On each occasion x-rays were taken to make sure of the proper position of the catheter.

In addition to the nineteen animals mentioned above, six normal dogs were injected intrabronchially, once a day for 4 to 7 days, with corresponding amounts of sterile dog blood serum.

All the animals were killed in from 9 to 18 days after the first intrabronchial injection. The results are shown in Tables I to III.

TABLE I.

Dog No.	Pneumococci per kilo intrabronchially.	Serum per kilo intrabronchially. Daily, 4 to 7 injections.	Length of life after pneumococcus injections.	Lesion organization.		Lung culture.
				In 1/6 of lobe or over.	Few small areas.	
	cc.	*cc.*	*days*			
1	2.5	2.5	9	+		Sterile.
2	3	3	18	+		"
3	4	4	18	+		"
4	3.5	3.5	17	+		"
5	3.5	3.5	17	+		83 colonies of Gram-negative bacilli.
6	3	3	15		+	
7	3.5	3.5	17		+	
8	3.5	3.5	17		+	
9	2.8	2.8	15	−	−	
10	2.5	2.5	15	−	−	
11	3.5	3.5	17	−	−	
12	3.3	3.3	18	−	−	

TABLE II.

Dog No.	Pneumococci per kilo intrabronchially.	Length of life after pneumococcus injections.	Lesion organization.	
			In 1/6 of lobe or over.	Few small areas.
	cc.	*days*		
13	3.8	18	—	—
14	2.2	15	—	—
15	3.5	17	—	—
16	3.5	17	—	—
17	4.3	18	—	+
18	2.25	9	—	+
19	4	15	—	+

TABLE III.

Dog No.	Serum per kilo intrabronchially. Daily, 4 to 7 injections.	Length of life after first injection of serum.	Lesion organization.	
			In 1/6 of lobe or over.	Few small areas.
	cc.	*days*		
20	4.6	15	—	—
21	3.3	15	—	—
22	4.16	13	—	—
23	4.5	13	—	—
24	3.5	15	—	—
25	3.5	15	—	—

ILLUSTRATIVE PROTOCOL.

Dog 1.—Weight 12,000 gm.

May 22, 1916, 9.20 p.m. Catheter 17 F inserted into bronchus. X-ray taken (catheter in bronchus to right lower lobe). 30 cc. of 29 hour culture of Group I pneumococcus in broth injected through catheter.

May 25–30. 30 cc. of sterile dog blood serum injected daily through catheter in right lower lobe. X-rays taken before each injection.

May 31, 4 p.m. Animal etherized.

Autopsy.—Performed at once. Right lower lobe much more voluminous than normal. Large, solid masses palpable. On section numerous small and larger solid, heavy, airless, consolidated areas are made out, involving one-half of lobe. One area in center the size of small walnut; one near periphery the size of a large walnut. Other areas smaller. These solid patches have a smooth surface and have a grayish red appearance. In branches of the bronchus of this lobe there are firm grayish white plugs, in some places partially, in others completely occluding

the lumen. Histological examination shows the majority of the alveoli in the consolidated portion partially filled with wandering cells (large mononuclear and polymorphonuclear), varying amounts of fibrin, and numerous fibroblasts, in many places associated with fresh capillaries. The process is strikingly shown in the bronchioles where the fibroblasts and fresh capillaries invading the retained exudate are very prominent.

Film preparations of the lung culture taken at the time of autopsy (five loops of expressed tissue juice) on blood agar showed no growth at the end of 3 days.

It will be seen from Table I that in the majority of animals receiving repeated injections of the serum into the pneumonic lung, complete resolution did not occur. In most of these, 9 to 18 days after the production of pneumonia, areas of consolidation in one-sixth or over of a lobe, were present, and microscopically the exudate in the bronchioles and alveoli of the consolidated portions showed extensive organization. In several of the animals the areas of organizing pneumonia were smaller. (Figs. 1 to 5.)

Cultures taken from the lung, in which areas of consolidation were present in one-sixth or more of a lobe, showed no growth in four of the five cases. In the fifth a number of colonies of a Gram-negative bacillus were obtained.

In the majority of dogs with pneumonia not treated with serum, complete resolution occurred (Table II). In two of the three animals in which complete resolution did not occur, no macroscopic areas were observed at the time of autopsy, but a study of the sections showed a small number of alveoli containing exudate undergoing organization. In the third animal there were about twelve pin-head to lentil-sized areas. Most of these showed microscopically an exudate of polymorphonuclear leukocytes, mononuclear cells, scattered red blood cells, and little fibrin. The areas showing organization of the exudate were no more extensive than in the two mentioned above.

In the animals receiving repeated doses of serum alone (Table III) no areas of consolidation were found at autopsy, and microscopically the lungs showed no exudate of any kind.

CONCLUSION.

The experiments reported above give evidence that in unresolved lobar pneumonia, the persistence of the exudate, followed by organization, depends upon the presence of serum in the exudate.

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EXPLANATION OF PLATES.

PLATE 17.

FIG. 1. Bronchiole showing persistent exudate undergoing organization, with attachment to the wall in three places. Dog 2, intrabronchial injection of pneumococci, followed by five daily injections of serum. Killed 18 days after onset of pneumonia. Magnification about 260.

FIG. 2. Alveoli and bronchioles containing persistent exudate undergoing organization. Dog 3, intrabronchial injection of pneumococci, followed by five daily injections of serum. Killed 18 days after onset of pneumonia. Magnification about 260.

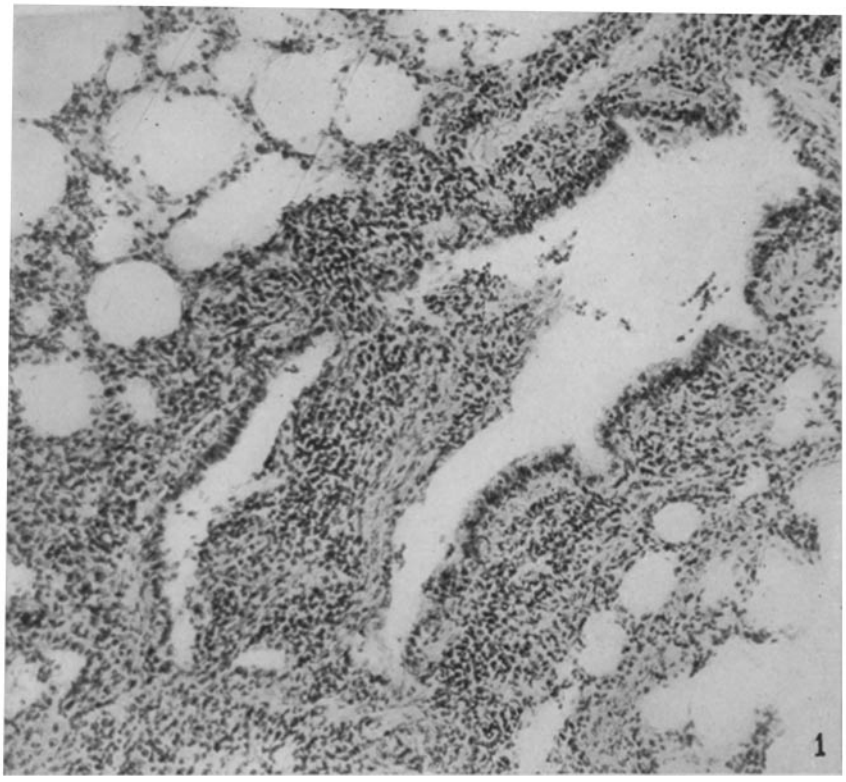
PLATE 18.

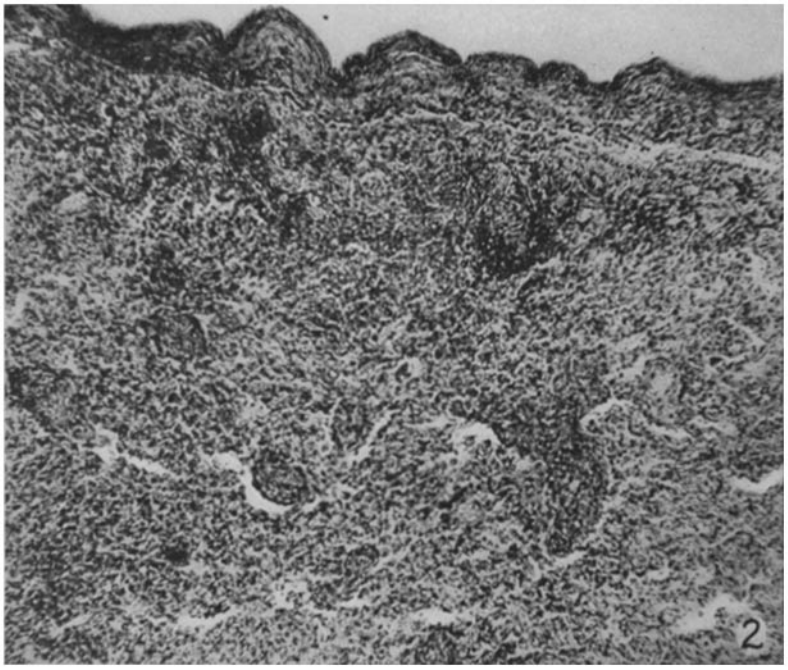
FIG. 3. Alveoli and bronchioles containing persistent exudate undergoing organization, showing extension of process through the pores of Kohn. Dog 3. Magnification about 260.

FIG. 4. High power of portion of the same section as Fig. 1 (Dog 2), showing attachment of exudate to bronchiole wall and ingrowth of fibroblasts. Magnification about 800.

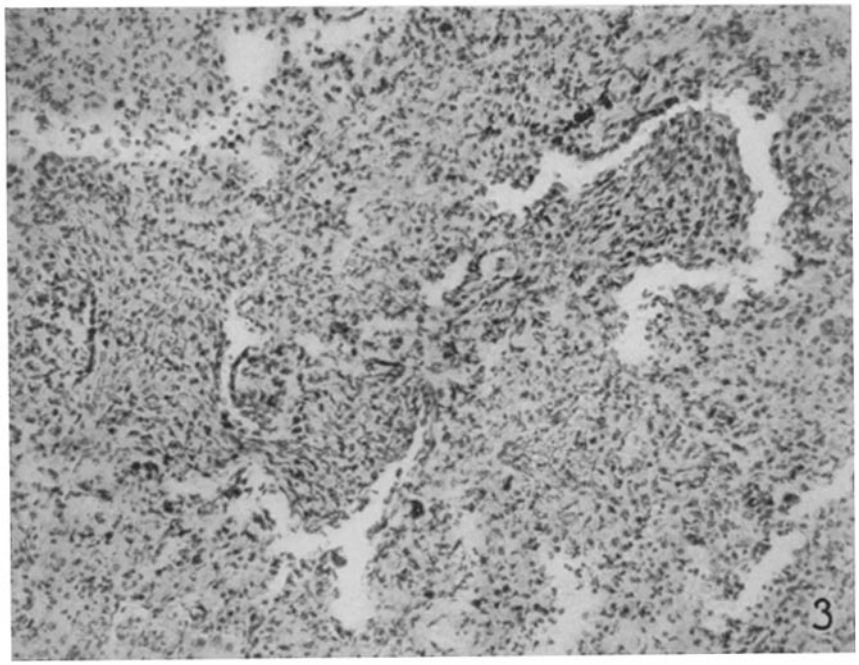
PLATE 19.

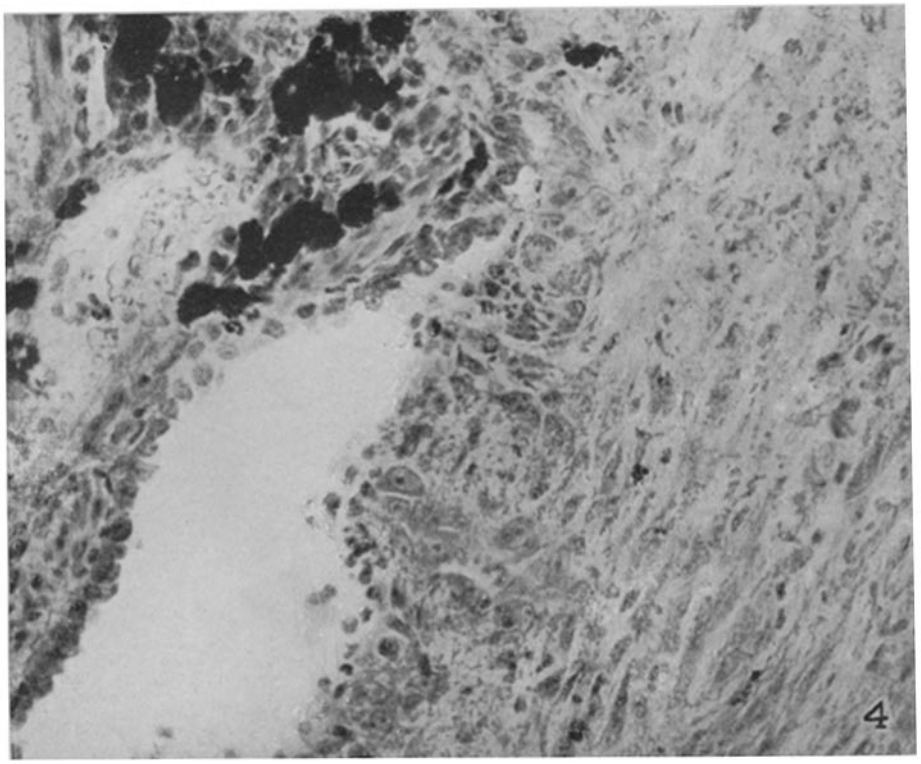
FIG. 5. Another portion of same section as Fig. 1 (Dog 2), showing attachment of exudate to wall and ingrowth of fibroblasts and capillary. Magnification about 800.





(Kline: Organization in lobar pneumonia.)





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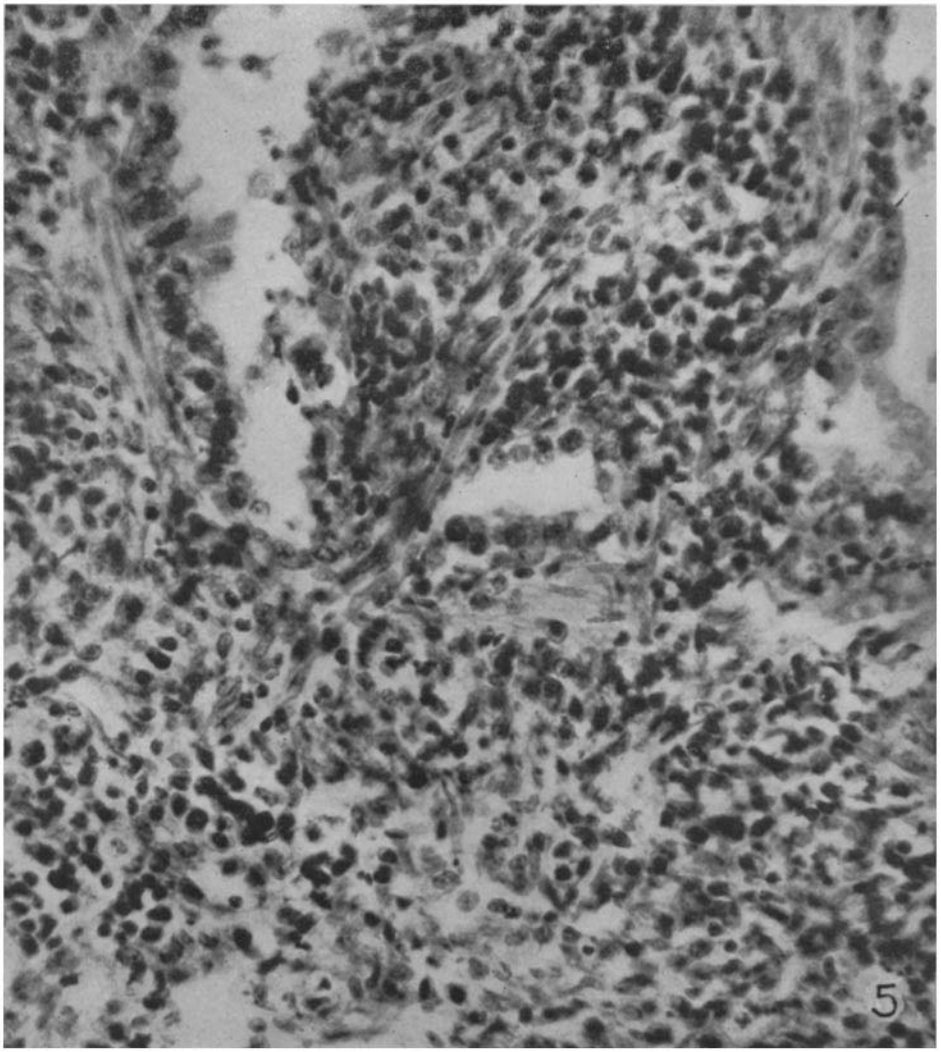

(Kline: Organization in lobar pneumonia.)