STUDIES ON EXPERIMENTAL PNEUMONIA.*

I. Production of Pneumococcus Lobar Pneumonia in Monkeys.

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INTRODUCTION.

The unusual prevalence of pneumonia during the past 2 years has led to much intensive study of the disease. Perhaps the most important contributions to these studies have been the increasing emphasis laid upon etiologic classification of pneumonia, the correlation of the clinical features and pathology of the disease with the various bacteria that are capable of producing it, and the indication that prophylactic vaccination against certain types of pneumococcus pneumonia may lead to a reduction in the incidence of these types.

The different biologic types of pneumococcus, *Streptococcus hæmolyticus*, and *Bacillus influenzæ* have been the organisms most frequently associated with the pneumonia that has occurred. While it has been found possible to differentiate to a considerable extent the clinical features and pathology of the various types of pneumonia caused by these different bacteria, many points have remained obscure because of the frequent occurrence of mixed infections, especially in the pneumonia that has followed influenza. Perhaps the greatest difference in opinion has arisen with respect to the relation of *Bacillus influenzæ* to epidemic influenza and to the pneumonia which so frequently complicates it. Similarly, though the results of prophylactic vaccina-

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tion against pneumococcus pneumonia strongly suggest that a definite degree of immunity against lobar pneumonia is provided by this procedure, the interpretation of statistical studies upon the incidence of disease in man is always difficult because of uncontrollable and apparently unrelated factors that may influence the outcome of the experiment.

It seemed possible that more definite knowledge might be obtained concerning the various types of pneumonia and the efficiency of prophylactic vaccination if a study of experimental pneumonia were undertaken, since by this means pure infections might be dealt with and adequate experimental controls would be available. In addition, a study of the therapeutic efficiency of Type I antipneumococcus serum and of an outbreak of spontaneous pneumonia among the stock animals was conducted.

Since it had been previously found[1] that experimental pneumonia could readily be produced in the monkey by the intratracheal injection of small amounts of culture, this animal was selected as offering the best opportunity for success. Two species of monkeys have been used, *Macacus syrichtus* from the Philippine Islands and *Cebus capucinus* from Central America. All were fresh stock and had not previously been kept in captivity in this country. Normal animals were used throughout, no preliminary procedures to lower resistance or to produce injury to the respiratory tract being resorted to except in a few instances for special purposes as indicated in the text. The results of the study will be reported in a series of papers.[2]

[1] Opie, E. L., Freeman, A. W., Blake, F. G., Small, J. C., and Rivers, T. M., unpublished experiments.

[2] The present paper is the first of this series; Paper II follows. The others will appear in later numbers of this *Journal*. Their titles are as follows: III. Spontaneous pneumonia in monkeys. IV. Results of prophylactic vaccination against pneumococcus pneumonia in monkeys. V. Active immunity against experimental pneumococcus pneumonia in monkeys following vaccination with living cultures of pneumococcus. VI. Active immunity following experimental pneumococcus pneumonia in monkeys. VII. Treatment of experimental Pneumococcus Type I pneumonia in monkeys with Type I antipneumococcus serum. VIII. Experimental *Streptococcus hæmolyticus* pneumonia in monkeys. IX. Production of influenza in monkeys by inoculation with *Bacillus influenzæ*. X. Pathology of experimental influenza and of *Bacillus influenzæ* pneumonia in monkeys.

Pneumococcus Lobar Pneumonia.

Many attempts have been made to produce lobar pneumonia in animals.[3] In the instances in which a lobar consolidation of the lung has been successfully produced, the results have not been altogether satisfactory either because it has not been clearly shown that the animals suffered from clinical lobar pneumonia as seen in man, or because large amounts of culture material were injected under more or less artificial conditions, or because various preliminary procedures injurious to the respiratory tract were resorted to in order to render the animal susceptible to infection. In the present experiments the attempt has been made to avoid these objections in as far as was possible, while at the same time a method of inoculation was employed that would consistently produce the desired result.

Four highly virulent strains of pneumococcus have been used throughout. Three of these were stock laboratory strains originally isolated from cases of lobar pneumonia of Pneumococcus Type I, Pneumococcus Type II, and Pneumococcus Type III respectively, of which 0.0000001 cc. of an 18 hour broth culture injected intraperitoneally regularly killed white mice within 48 hours. The fourth was a pneumococcus of Type IV isolated at autopsy from a monkey dying of spontaneous lobar pneumonia. This pneumococcus killed white mice within 48 hours when injected intraperitoneally in doses of 0.000001 cc. of an 18 hour broth culture.

Methods.

The method of inoculation was by direct intratracheal injection, under aseptic precautions, by the insertion of a small caliber, dry, sterile needle into the lumen of the trachea between the tracheal cartilages just below the larynx and the introduction of the culture by means of a Luer glass syringe inserted into the stock of the needle.

[3] Wadsworth, A., *Am. J. Med. Sc.*, 1904, cxxvii, 851. (This article contains a review of the older literature.) Lamar, R. V., and Meltzer, S. J., *Proc. Soc. Exp. Biol. and Med.*, 1909–10, vii, 102; *J. Exp. Med.*, 1912, xv, 133. Wollstein, M., and Meltzer, S. J., *J. Exp. Med.*, 1912, xvi, 126. Winternitz, M. C., and Hirschfelder, A. D., *J. Exp. Med.*, 1913, xvii, 657. Sisson, W. R., and Walker, I. C., *J. Exp. Med.*, 1915, xxii, 747.

The procedure is relatively simple, takes but a few seconds, subjects the animal to a minimal amount of trauma, and is not attended by gagging or coughing. In no instance at autopsy has there been any evidence of local injury or infection in the trachea or in the tissue surrounding it. The amounts of culture injected ranged from 0.000001 to 1 cc. of an 18 hour plain broth culture. A constant amount of fluid, 1 cc., was used throughout, dilutions of cultures being made in plain broth.

The methods of study after inoculation consisted in observation and record of clinical symptoms and physical signs, the taking of morning and afternoon temperature (rectal), daily counts of the white blood corpuscles with examination of stained blood films and differential white blood counts, and daily blood cultures in broth and in poured agar plates with record of the number of pneumococcus colonies developing per 0.5 cc. of blood. No record of the pulse or respiration rate was kept, since it was not found feasible to record these accurately. X-ray plates were taken in a few instances (Figs. 1 and 2), but no systematic study was made. Autopsies with bacteriological examination were performed on all animals that died or were killed.

EXPERIMENTAL.

Production of Lobar Pneumonia by the Intratracheal Injection of Pneumococcus.

Thirty-seven normal monkeys were injected intratracheally with cultures of pneumococcus in amounts ranging from 1 to 0.000001 cc. of an 18 hour broth culture, a constant amount of fluid, 1 cc., being used in all the experiments. Pneumococcus Type I was used thirty-one times; Pneumococcus Type II, twice; Pneumococcus Type III, three times; and Pneumococcus Type IV, once. In thirty-two instances lobar pneumonia in all its aspects resembling the disease as seen in man was successfully produced. In five cases the monkeys failed to develop pneumonia. The results are shown in Table I.

It will be seen from the data presented in Table I that pneumonia was as readily produced by the injection of 0.000001 cc. of pneumococcus as with larger amounts. Of the twenty-six monkeys in which

lobar pneumonia was produced with Pneumococcus Type I, twenty-one died, and five recovered, the latter all receiving amounts of less than 0.001 cc. With the exception of the fact that all the monkeys which received 0.001 cc. of culture or more died, there is no evident relation between the duration of the disease and final outcome on the one hand and the weight of the monkey or amount of culture injected on the other. The differences probably depended upon individual variation in resistance to pneumococcus infection.

Although the strains of Pneumococcus Type II, Type III, and Type IV used were as virulent for mice as the strain of Pneumococcus Type I, they proved much less so for monkeys. Of the six monkeys injected with these organisms all recovered, although a relatively large amount of culture, 0.1 to 1 cc., was used.

No attempt is made to explain the failure to produce pneumonia in five animals. Monkey 4 died in 23½ hours with an overwhelming septicemia. Monkey 27 died on the 3rd day with an acute fibrinopurulent pneumococcus pericarditis and overwhelming septicemia. Monkeys 63, 76, and 128, all of which received minute amounts of culture, showed no evidence of infection.

In addition to the cases shown in Table I, lobar pneumonia was successfully produced in a similar manner in twenty-nine other experiments, twenty times with Pneumococcus Type I, twice with Pneumococcus Type II, twice with Pneumococcus Type III, and five times with Pneumococcus Type IV. These monkeys had either been vaccinated previously with pneumococcus vaccine, or had had a preceding attack of pneumonia, or were treated with antipneumococcus serum, and therefore, although they were in normal health at the time of injection, they are excluded from the series of normal animals shown in Table I. Experiments dealing with them will be presented in Papers IV to VII. The clinical records of some, however, are included in this paper in order to illustrate certain features of the disease.

In the following paragraphs abbreviated protocols illustrative of the clinical features of the pneumonia experimentally produced in monkeys are presented, study of the pathology of the disease being reserved for Paper II. Since many of the experiments were entirely similar, it has not seemed necessary to give the protocols of all, those

TABLE I.

Effect of Intratracheal Inoculation of Monkeys with Pneumococcus.

Monkey No.	Species.	Weight.	Date of inoculation.	Type of pneumococcus.	Amount of culture.	Clinical diagnosis.	Result.	Autopsy.
		gm.	*1919*		*cc.*			
1	*C. capucinus.*	1,746	Feb. 17	I	1.0	L. P.*	Died on 2nd day.	Lobar pneumonia, R. L.;† engorgement and red hepatization.
2	" "	1,290	" 24	I	0.5	"	" in 12½ hrs.	Lobar pneumonia, R. U., R. L., L. U., L. L.; engorgement and red hepatization.
3	" "	1,595	" 24	I	0.1	"	" on 2nd day.	Lobar pneumonia, L. U., L. L.; engorgement and red hepatization.
4	" "	1,835	" 26	I	0.01	?	" in 23½ hrs.	No pneumonia. Pneumococcus septicemia.
5	" "	1,410	Mar. 5	I	0.01	L. P.	" " 23¼ hrs.	Lobar pneumonia, R. U., R. L., L. L.; engorgement and red hepatization.
6	" "	1,960	" 5	I	0.001	"	" on 4th day.	Lobar pneumonia, R. U., R. L.; engorgement and red hepatization; acute fibrinous pleuritis, right.
23	*M. syrichtus.*	3,555	" 18	I	1.0	"	" " 5th "	Lobar pneumonia, L. L., engorgement and red hepatization; R. L., engorgement; acute fibrinous pleuritis, left.
26	" "	2,680	" 21	I	1.0	"	Dying, killed 9th day.	Lobar pneumonia, R. L., L. L.; gray hepatization; acute fibrinous pleuritis, right and left.
27	" "	2,620	" 26	I	1.0	P. S.	Died on 3rd day.	Acute fibrinopurulent pericarditis; pneumococcus septicemia; no pneumonia.
29	" "	3,920	Apr. 2	I	1.0	L. P.	" " 2nd "	Lobar pneumonia, L. U., L. M., L. L.; engorgement and red hepatization; acute fibrinous pleuritis, left.

30	*M. syrichtus.*	4,120	Apr. 2	I	0.1	L. P.	Died on 12th day.	Lobar pneumonia, R. U., R. M., R. L., L. U., L. M., L. L.; gray hepatization and beginning resolution; acute fibrinous pleuritis, right and left; dilatation of heart.
31	" "	3,850	" 2	I	0.01	"	" " 10th "	Lobar pneumonia, L. U., L. M., L. L.; gray hepatization; empyema, left; acute purulent mediastinitis.
25	*C. capucinus.*	740	" 4	II	0.1	"	Recovered by crisis on 7th day. Killed.	Lobar pneumonia, R. U.; gray hepatization and beginning resolution; acute fibrinous pleuritis, right.
42	*M. syrichtus.*	4,955	" 10	I	0.001	"	Died on 37th day.	Lobar pneumonia, L. M., L. L., organization; R. U., R. M., R. L., partial resolution and organization; chronic fibrous pleuritis, right and left.
63	" "	2,100	" 19	I	0.000001	‡	Remained well.	No autopsy.
75	" "	4,200	" 29	I	0.0001	L. P.	Recovered by crisis on 12th day.	" "
76	" "	4,600	" 29	I	0.00001	‡	Remained well.	" "
77	" "	2,600	" 29	I	0.000001	L. P.	Recovered by crisis on 11th day.	" "
82	*C. capucinus.*	730	" 30	III	0.1	"	Recovered by crisis on 7th day. Killed.	Interstitial pneumonia, R. U.; resolving.
83	*M. syrichtus.*	2,470	" 30	I	0.001	"	Died on 8th day.	Lobar pneumonia, R. U., R. M., R. L.; red and gray hepatization; acute serofibrinous pleuritis, right.
85	" "	2,675	May 6	I	0.001	"	" " 6th "	Lobar pneumonia, L. M., L. L.; engorgement and red hepatization; acute fibrinous pleuritis, left.

* L. P indicates lobar pneumonia; P. S., pneumococcus septicemia.

† R. L., R. M., R. U., etc., indicate lobes of the lung. The cardiac lobe is included as part of the right lower lobe.

‡ No disease.

TABLE I—*Concluded.*

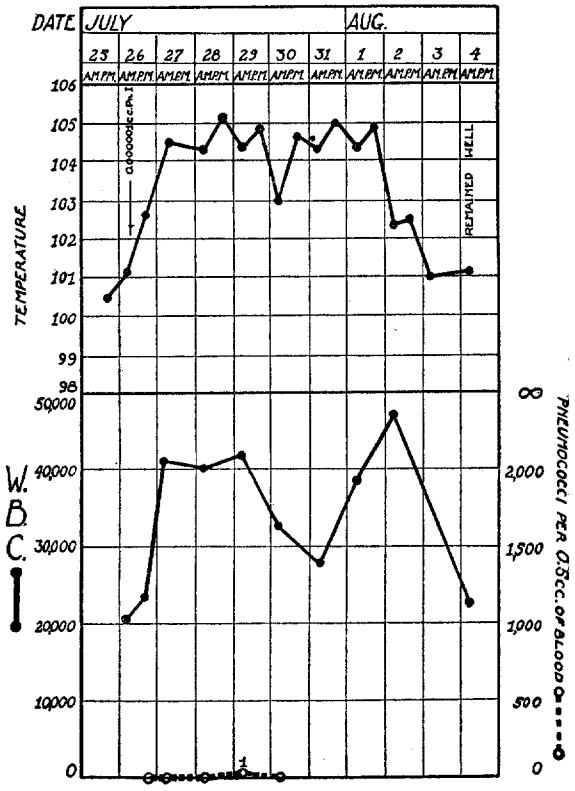
Monkey No.	Species.	Weight.	Date of inoculation.	Type of pneumococcus.	Amount of culture.	Clinical diagnosis.	Result.	Autopsy.
		gm.	*1919*		*cc.*			
86	*M. syrichtus.*	2,424	May 6	I	0.000001	L. P.	Died on 14th day.	Lobar pneumonia, R. L., L. L.; gray hepatization; acute fibrinous pleuritis, right and left.
87	" "	2,835	" 6	I	0.1	"	" " 5th "	Lobar pneumonia, L. U., L. M., L. L., red hepatization; R. L., engorgement; acute fibrinous pleuritis, left.
95	" "	4,100	" 13	I	0.00001	"	Recovered by crisis on 11th day. Relapse (?) on 15th day. Recovery by crisis on 21st day. Killed.	Lobar pneumonia, L. L.; partial resolution and organization; organizing pleuritis, left.
96	" "	2,655	" 13	I	0.000001	"	Recovered by crisis on 9th day.	No autopsy.
93	" "	5,110	" 15	I	0.001	"	Died on 13th day.	Lobar pneumonia, R. U., R. M., R. L.; gray hepatization; acute fibrinous pleuritis, right; hypertrophy and dilatation of heart.
98	" "	4,100	" 20	I	0.000001	"	" " 4th "	Lobar pneumonia, R. U., R. L., L. U., L. L.; engorgement.
109	" "	4,585	" 27	I	0.001	"	" " 3rd "	Lobar pneumonia, R. U., R. M., L. U., L. M.; engorgement.
110	" "	2,710	" 27	I	0.000001	"	" " 7th "	Lobar pneumonia, R. U., R. M., R. L.; red and gray hepatization; acute fibrinopurulent pericarditis; acute fibrinous pleuritis, right.

111	*M. syrichtus.*	2,220	June 27	IV	0.1	L. P.	Recovered by crisis on 11th day.	No autopsy.
112	" "	3,975	" 5	I	0.01	"	Died on 6th day.	Lobar pneumonia, R. M., R. L., red and gray hepatization; L. L., engorgement; acute fibrinous pleuritis, right.
114	" "	3,000	" 20	I	0.000001	"	" " 5th "	Lobar pneumonia, R. L., L. L.; engorgement.
91	" "	4,005	" 24	II	0.1	"	Recovered by crisis on 18th day.	No autopsy.
115	" "	3,015	" 24	III	0.1	"§	Recovered by lysis on 3rd day.	" "
107	" "	2,335	July 1	III	1.0	"§	Recovered by lysis on 4th day. Killed.	Interstitial pneumonia, R. L.; acute fibrinous pleuritis, right.
127	" "	2,700	" 24	I	0.000001	"	Recovered by crisis on 8th day.	No autopsy.
128	" "	2,650	" 26	I	0.000001	‡	Remained well.	" "

§ Abortive.

presented having been selected with the purpose of bringing out as fully as possible the various aspects of the disease. The temperature, white blood counts, and results of blood cultures are shown in Text-figs. 1 to 17.

Experiment 1. Monkey 115 (Text-Fig. 1).—Macacus syrichtus, female; weight 3,015 gm. Previously inoculated with Pneumococcus Type III on June 24, and



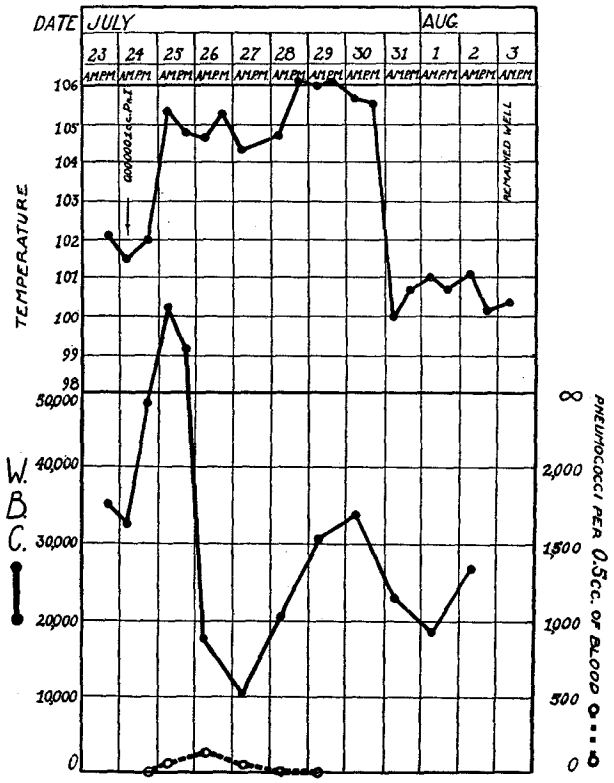
TEXT-FIG. 1. Monkey 115. Experimental lobar pneumonia following the intratracheal injection of 0.000001 cc. of Pneumococcus Type I broth culture.

with Pneumococcus Type IV on July 1, 1919. July 25. Well and active. July 26, 10.20 a.m. Intratracheal injection of 0.000001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. 4 p.m. Appears well. July 27. Moderately sick; respirations rapid and labored, with expiratory grunt. July 28. Condition the same. July 29. Quite sick; no appetite; breathing rapidly; coughs frequently.

Dullness and suppressed breath sounds over right lower lobe. July 30 to Aug. 1. Condition the same. Aug. 2. Appears well and active; breathing easily; temperature fallen to normal by crisis. Aug. 4. Continues well.

Diagnosis.—Lobar pneumonia, right lower lobe.

Experiment 2. Monkey 117 (Text-Fig. 2).—Macacus syrichtus, male; weight 2,565 gm. July 23, 1919. Well and active. July 24, 11 a.m. Intratracheal injection of 0.000001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type

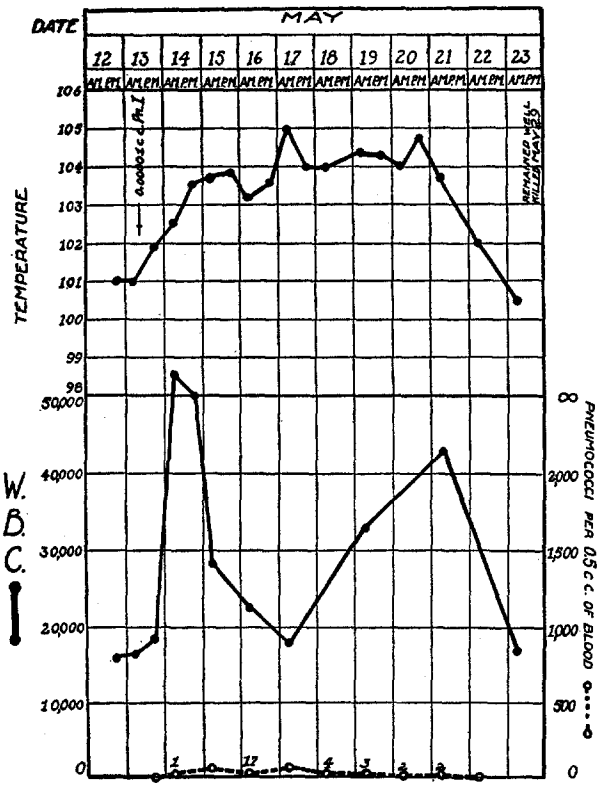


TEXT-FIG. 2. Monkey 117. Experimental lobar pneumonia following the intratracheal injection of 0.000001 cc. of Pneumococcus Type I broth culture.

I. 4.30 p.m. Appears well. July 25, 11 a.m. Shivering violently. Respirations accelerated. July 26. Sick; respirations rapid and labored; lungs clear. July 27. Condition the same. July 28. Refuses food; breathing rapidly; dullness over right lower lobe. July 29. Condition the same. Marked dullness, suppressed breathing, and fine moist râles over right lower lobe; coughs occasionally. July 30. Condition the same. July 31. Appears well; breathing easily; temperature fallen to normal by crisis. Aug. 5. Continues well.

Diagnosis.—Lobar pneumonia, right lower lobe.

Experiment 3. Monkey 81 (Text-Fig. 3).—*Macacus syrichtus*, female; weight 2,750 gm. May 12, 1919. Well and active. May 13, 10.55 a.m. Intratracheal injection of 0.00001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. 4.20 p.m. Appears well. May 14. Quiet but otherwise appears well. May 15. Moderately sick; breathing rapidly. May 16 to 18. Condition the same. May 19 to 22. Appears sicker; huddled up leaning against side of cage; respira-



TEXT-FIG. 3. Monkey 81. Experimental lobar pneumonia following the intratracheal injection of 0.00001 cc. of Pneumococcus Type I broth culture.

tions rapid and labored. May 23. Appears much better, but manifests considerable weakness and dyspnea on exertion; temperature normal. May 25. Appears stronger. May 29. Remains well. Killed.

Autopsy.—Lobar pneumonia, right middle and lower lobes, resolving; acute fibrinous pleuritis, right.

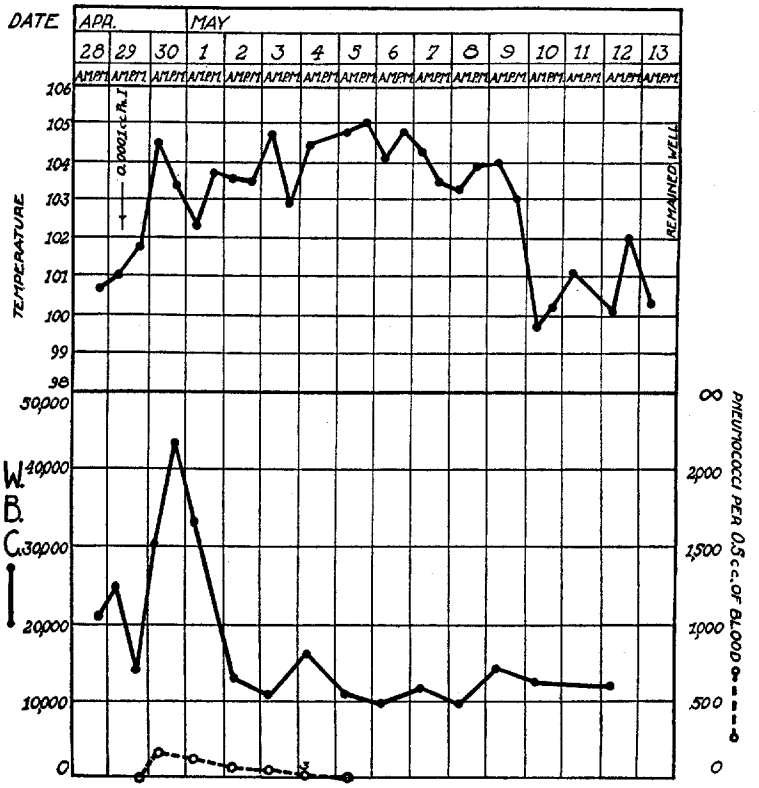
Cultures.—Heart's blood and right lower lobe, no growth.

Monkeys 115, 117, and 81 show well the characteristic clinical features of relatively mild lobar pneumonia with recovery. It will be noted that the temperature curves are identical with those of similar cases in man, presenting the features of sudden onset, sustained elevation throughout the course of the disease, and a critical fall to normal on the 7th or 8th day. The characteristic chill at onset was observed in Monkey 117. In relatively mild pneumonia such as these cases represent monkeys appear only moderately sick, sitting up throughout the course of the disease, and never exhibiting any degree of prostration. The clinical symptoms consist of characteristic rapid and labored respiration, often with expiratory grunt, infrequent cough rarely appearing before the latter half of the disease, and loss of appetite and activity. Monkeys 115 and 117 show a characteristic transient invasion of the blood by pneumococci with disappearance of the bacteremia several days before crisis. Monkey 81 shows a low grade bacteremia throughout the active stage of the disease, an uncommon feature in monkeys that recovered. The characteristic leucocyte curve in non-fatal pneumonia is well illustrated in all three cases. It consists of a preliminary high polymorphonuclear leucocytosis followed by a fall to normal, a secondary rise during the latter half of the disease, and a return to normal with crisis. It will be noted that the first fall of leucocytes to normal is approximately coincident with the peak of the bacteremia, a feature that has occurred with surprising constancy throughout the series of experiments. This type of leucocyte reaction has occurred in all monkeys that have recovered, with the exception of four in which the secondary rise was not demonstrated.

Experiment 4. Monkey 75 (Text-Fig. 4).—Macacus syrichtus, male; weight 4,200 gm. Apr. 28, 1919. Well and active. Apr. 29, 11.10 a.m. Intratracheal injection of 0.0001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. 5.10 p.m. Appears well. Apr. 30, 11 a.m. Sits huddled up, shivering; respirations slightly accelerated. May 1. Sick; refuses food; respirations rapid with expiratory grunt. Moderate dullness, diminished breath sounds, and fine moist râles in left lower axilla. May 2. Condition the same. Dullness and bronchial breathing over left lower lobe. May 3 to 8. Condition remains the same; coughs frequently. May 9. Improving. May 10. Seems well and active, though weak. Temperature fallen to normal by crisis. May 15. Remains well. X-ray photograph of chest shows an area of density in the left lower chest (Fig. 1).

Diagnosis.—Lobar pneumonia, left lower lobe.

Monkey 75 illustrates a prolonged severe case of lobar pneumonia with final recovery by crisis on the 12th day. The sudden onset with chill, the rapid respiration with expiratory grunt, and the physical signs are all characteristic of typical lobar pneumonia. The diagnosis was confirmed by x-ray. The absence of a secondary rise in the



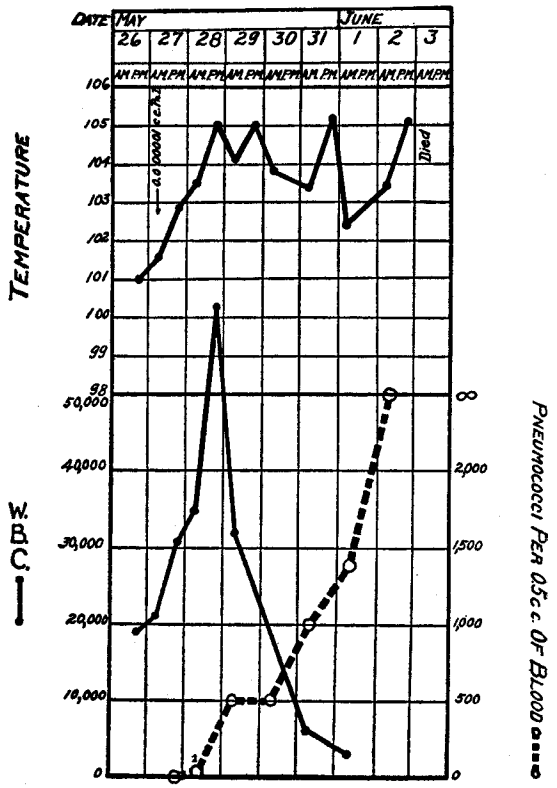
TEXT-FIG. 4. Monkey 75. Experimental lobar pneumonia following the intratracheal injection of 0.0001 cc. of Pneumococcus Type I broth culture.

leucocyte curve is illustrated in this case, a feature of unusual occurrence in monkeys that recovered.

Experiment 5. Monkey 110 (Text-Fig. 5).—Macacus syrichtus, female; weight 2,710 gm. May 26, 1919. Well and active. May 27, 10.20 a.m. Intratracheal injection of 0.000001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. May 28. Quiet; respirations rapid. May 29. Appears moderately

sick; refuses food; breathing rapidly. May 30. Condition the same. May 31 to June 1. Very sick; respirations rapid and labored; sits huddled up in corner of cage. June 2. Very sick; respirations rapid and gasping; lies down on floor of cage at times. June 3. Found dead in morning.

Autopsy.—Lobar pneumonia, right upper, middle, and lower lobes; red and gray hepatization; acute fibrinopurulent pericarditis; acute fibrinous pleuritis, right; cardiac dilatation.

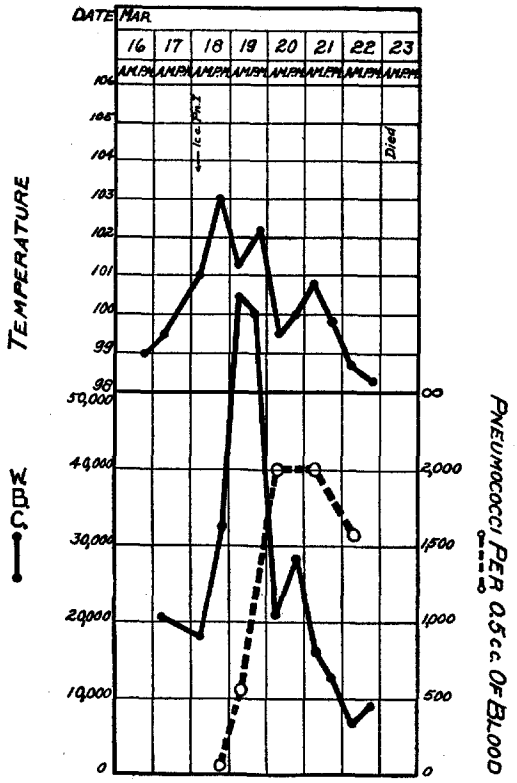


TEXT-FIG. 5. Monkey 110. Experimental lobar pneumonia following the intratracheal injection of 0.000001 cc. of Pneumococcus Type I broth culture.

Cultures.—Heart's blood, bronchus, right lower lobe, and pericardial fluid, Pneumococcus Type I.

Experiment 6. Monkey 23 (Text-Fig. 6).—*Macacus syrichtus*, male; weight 3,555 gm. Mar. 17, 1919. Well and active. Mar. 18, 10 a.m. Intratracheal injection of 1 cc. of 18 hour broth culture of Pneumococcus Type I. Mar. 19, 10 a.m. Appears more quiet than usual, but appetite is good and animal moves about

2 p.m. Appears sick; breathing rapidly; lungs clear. X-ray of chest shows slightly increased density in the left mid-lung area. Mar. 20. Sick; respirations rapid and grunting; refuses food; abdomen distended and tense. Moderate dullness and distant breath sounds in left lower axilla. Mar. 21. Very sick; respirations rapid and labored. Examination of chest shows pleural friction rub, dullness, and faint bronchial breathing in left lower axilla. Mar. 22. Condition the same. Mar. 23. Found dead in morning.



TEXT-FIG. 6. Monkey 23. Experimental lobar pneumonia following the intratracheal injection of 1 cc. of Pneumococcus Type I broth culture.

Autopsy.—Lobar pneumonia, left lower lobe; engorgement and red hepatization; incipient lobar pneumonia, right lower lobe; acute fibrinous pleuritis, left.

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

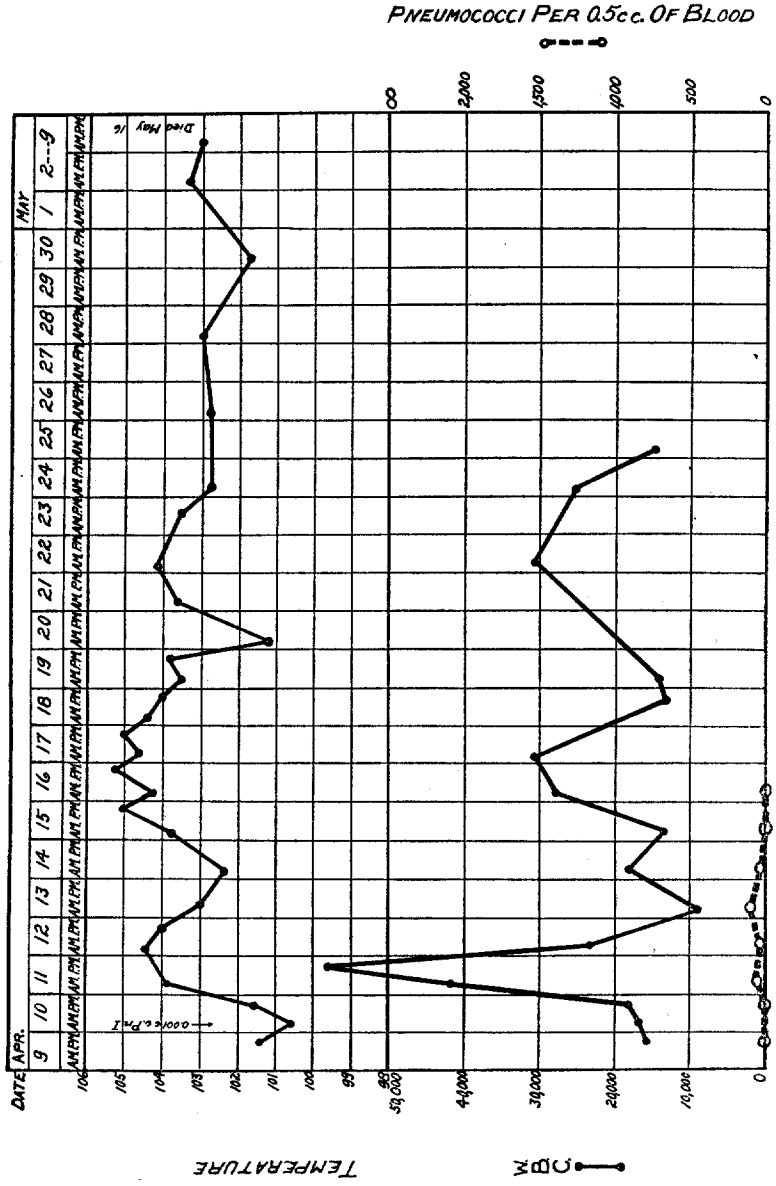
Monkeys 110 and 23 illustrate severe fatal cases of lobar pneumonia with overwhelming pneumococcus septicemia, Monkey 110

dying on the 7th day with complete consolidation of the right lung and a complicating pneumococcus pericarditis, and Monkey 23 dying on the 5th day with a moderately advanced lesion of the left lower lobe. The continued fall of the leucocyte curve with the development of a definite leucopenia coincident with the increasing septicemia has consistently occurred in cases of this nature. During this continued fall in leucocytes examination of stained blood films has shown increasing replacement of mature polymorphonuclear leucocytes by young forms until the former have practically disappeared from the blood. This has been accompanied in some instances by a terminal invasion of the blood by a few nucleated red blood corpuscles and other abnormal cells of the leucocyte series. It is noteworthy that even in the most severe cases of this kind monkeys show little evidence of prostration and maintain the sitting posture until within a relatively short time before death. Monkey 23 shows the unusual feature of a poor febrile reaction, an occurrence that is occasionally seen in rapidly fatal lobar pneumonia in man.

Experiment 7. Monkey 42 (Text-Fig. 7).—Macacus syrichtus, male; weight 4,955 gm. Apr. 9, 1919. Well and active. Apr. 10, 11 a.m. Intratracheal injection of 0.001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. Apr. 11. Appears well. Apr. 12. Moderately sick. Apr. 13. Sick; sits huddled up; breathing rapidly. Apr. 14. Condition the same. Dullness, suppressed breathing, fine moist râles, and pleural friction rub in right lower axilla. Apr. 16. Respirations rapid and labored; coughs occasionally. Dullness, bronchial breathing, and moist râles throughout both axillæ. Apr. 17 to 19. Condition the same. Apr. 20. Appears much better; temperature has fallen, but animal is still breathing rapidly. Apr. 22. Fails to improve. Temperature elevated. Apr. 28. No improvement. Continues to run an irregular fever. Slight exertion causes marked dyspnea. May 9. Animal growing progressively weaker; exhibits constant dyspnea which is greatly increased on exertion. Heart sounds loud and thumping; no murmurs. Dullness and loud bronchial breathing persist over left lower lobe; to and fro crackling râles are heard, probably pleural in origin. No evidence of empyema or pericarditis. May 10 to 15. Condition remains unchanged. May 16. Found lying on floor of cage in state of collapse. Respirations shallow and gasping. 11 a.m. Died.

Autopsy.—Lobar pneumonia, left lower and middle lobes, unresolved; right upper, middle, and lower lobes, nearly resolved; chronic fibrous pleuritis, left and right.

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



TEXT-FIG. 7. Monkey 42. Experimental lobar pneumonia, unresolved, following the intratracheal injection of 0.001 cc. of Pneumococcus Type I broth culture.

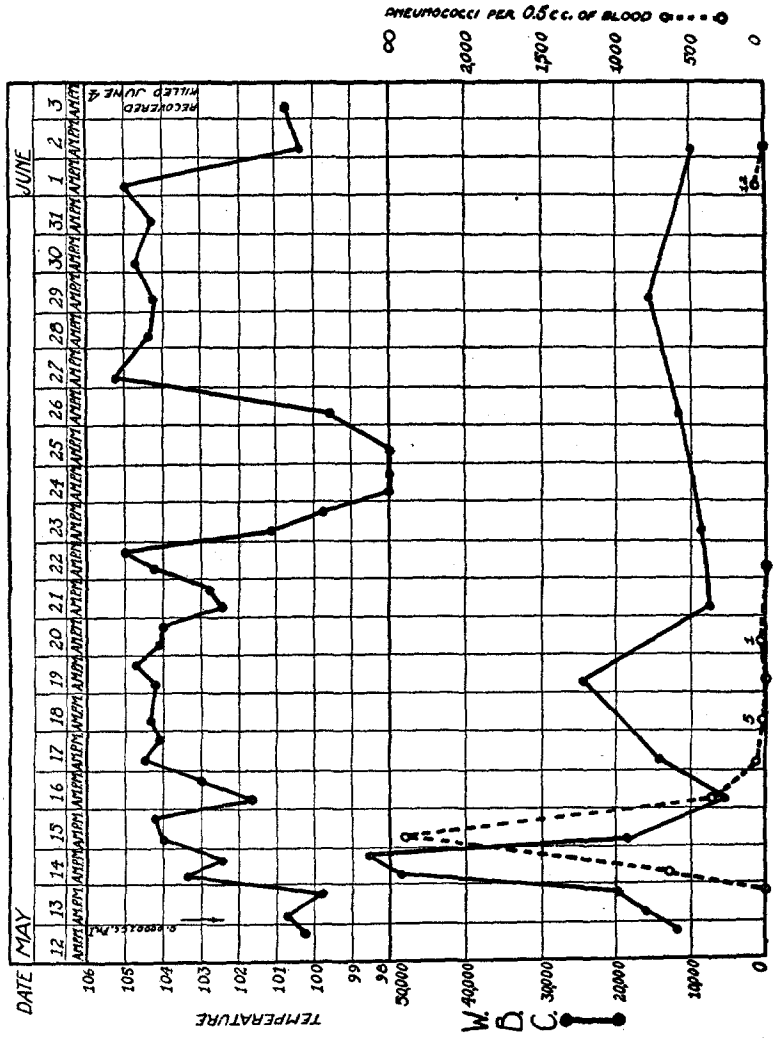
Monkey 42 illustrates a prolonged course due to an unresolved and organizing pneumonia with final death on the 37th day. The characteristic temperature curve with critical fall on the 11th day, and characteristic leucocyte reaction with fall to normal coincident with the peak of the septicemia and secondary rise are well shown. Following apparent recovery from the acute stage of the disease the monkey ran a continuous irregular temperature, manifested extreme weakness and constant shortness of breath on slight exertion, and showed persisting physical signs of consolidation in the left lower lobe. An instructive feature of the autopsy was the finding of pneumococci still present in the unresolved left lower lobe and in the heart's blood, the latter probably being a terminal invasion.

Experiment 8. Monkey 95 (Text-Fig. 8).—Macacus syrichtus, male; weight 4,100 gm. May 12, 1919. Well and active. May 13, 11.05 a.m. Intratracheal injection of 0.00001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. May 14. Quiet; respirations moderately accelerated. May 15 and 16. Appears sick; respirations rapid and grunting. May 17. Dullness and suppressed breath sounds over right lower lobe. May 18 to 22. Sick; respirations rapid and labored. May 23. Temperature fallen by crisis; appears much better. May 26. In good condition. May 27. Quiet; temperature elevated. May 28. Appears sick; huddled up in corner of cage; breathing rapidly. May 31. Condition remains the same. No evidence of pericarditis or empyema. June 2. Temperature fallen by crisis; appears better. June 4. Continues well. Killed.

Autopsy.—Lobar pneumonia, left lower lobe; pleuritis, left.

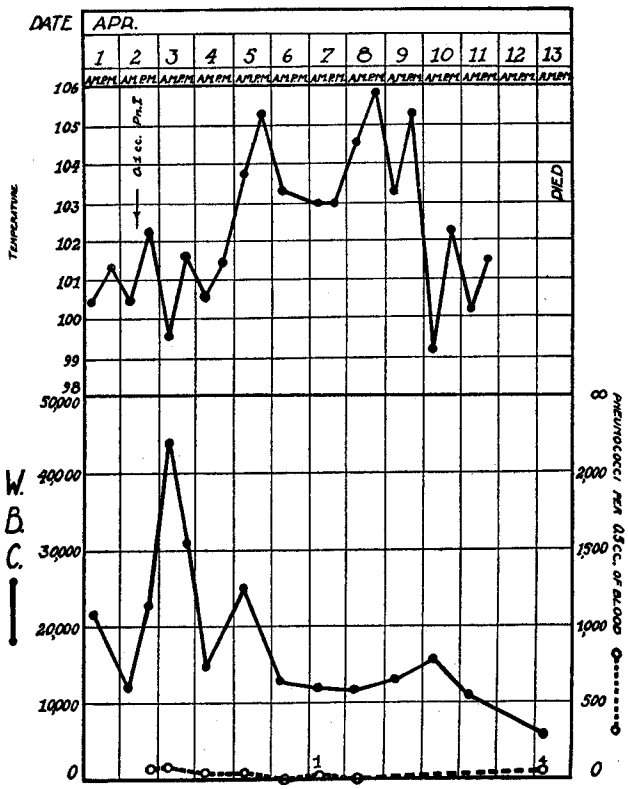
Cultures.—Heart's blood and left lower lobe, no growth.

Monkey 95 presents two unusual features. The first is that of recovery in spite of a very heavy early invasion of the blood stream by pneumococci. This has occurred in few instances. The second is an apparent relapse with a second attack of pneumonia beginning on the 4th day after recovery from the first attack. Examination of the chest during the first attack showed evidence of consolidation in the right lower lobe. It is possible, however, that this was a mistaken diagnosis since autopsy showed only a partially resolved pneumonia of the left lower lobe. There was no evidence of any complication. That the second attack was due to Pneumococcus Type I is shown by the isolation of that organism from the blood on June 1.



TEXT-FIG. 8. Monkey 95. Experimental lobar pneumonia, with relapse, following the intratracheal injection of 0.00001 cc. of Pneumococcus Type I broth culture.

Experiment 9. Monkey 30 (Text-Fig. 9).—Macacus syrichtus, male; weight 4,120 gm. Apr. 1, 1919. Well and active. Apr. 2, 11.10 a.m. Intratracheal injection of 0.1 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. Apr. 3. Appears well. Apr. 4. Moderately sick; breathing rapidly; breath sounds suppressed over left lower lobe. Apr. 5 to 7. Condition the same. Apr. 8. Sicker; respirations rapid and grunting. Examination of chest shows



TEXT-FIG. 9. Monkey 30. Experimental lobar pneumonia following the intratracheal injection of 0.1 cc. of Pneumococcus Type I broth culture. Death from cardiac dilatation (?).

dullness and loud bronchial breathing throughout left axilla, pleural friction rub, moderate dullness, and distant bronchial breathing in right lower front and axilla. Apr. 10. Appears better, but still weak and breathing rapidly. Temperature fallen by crisis. Apr. 11 and 12. Condition the same. Apr. 13, 11.30 p.m. Sudden collapse and death.

Autopsy.—Lobar pneumonia, all lobes; gray hepatization; acute fibrinous pleuritis, bilateral; cardiac hypertrophy and marked dilatation of right auricle and ventricle.

Cultures.—Heart's blood and lungs, no growth.

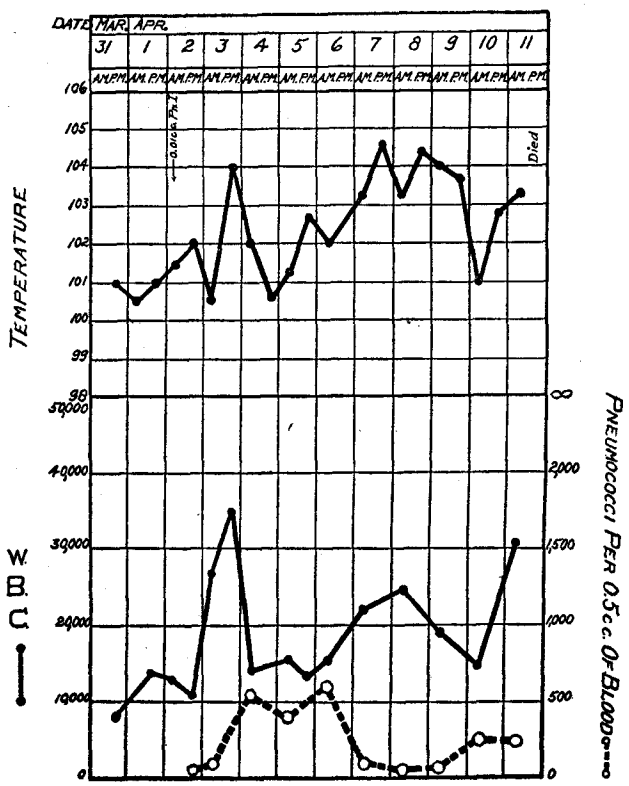
Monkey 30 likewise illustrates two unusual features. The first is an apparent delay in onset of the disease as manifested by symptoms and temperature reaction. It is noteworthy, however, that pneumococci had invaded the blood within 6 hours after intratracheal injection and that the preliminary leucocytosis was completed before there was clinical evidence that the monkey had developed pneumonia. The second is apparent recovery with crisis on the 8th day after inoculation, but death on the 12th day, autopsy revealing extensive consolidation involving all the lobes and marked dilatation of the heart. Cultures from the lungs and heart's blood remained sterile.

Experiment 10. Monkey 31 (Text-Fig. 10).—Macacus syrichtus, female; weight 3,850 gm. Apr. 1, 1919. Well and active. Apr. 2, 11.45 a.m. Intratracheal injection of 0.01 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. Apr. 3. Appears quiet but otherwise well. Apr. 4. Moderately sick; no appetite; respirations rapid. Apr. 6. Sicker; respirations very rapid and grunting. Apr. 8. Condition the same. Dullness, fine moist râles, and bronchial breathing over left lower and middle lobes. Apr. 9. Coughs occasionally. Apr. 10. Condition the same; pleural friction rub in left axilla. X-ray shows a dense shadow in the fourth and fifth left interspaces. Apr. 11. Very sick; respirations deep and gasping. 3 p.m. Died.

Autopsy.—Lobar pneumonia, left upper, middle, and lower lobes; gray hepatization; localized empyema, left; acute purulent mediastinitis.

Cultures.—Heart's blood, bronchus, and empyema, Pneumococcus Type I; left lower lobe, no growth.

Monkey 31 represents lobar pneumonia complicated by empyema. The inverse relation between the degree of leucocytosis and the degree of septicemia during the acute stage of the disease is quite striking. A persistent septicemia with rising leucocyte count during the latter part of the disease as shown in this case has nearly always been associated with the development of a complication such as empyema or pericarditis.



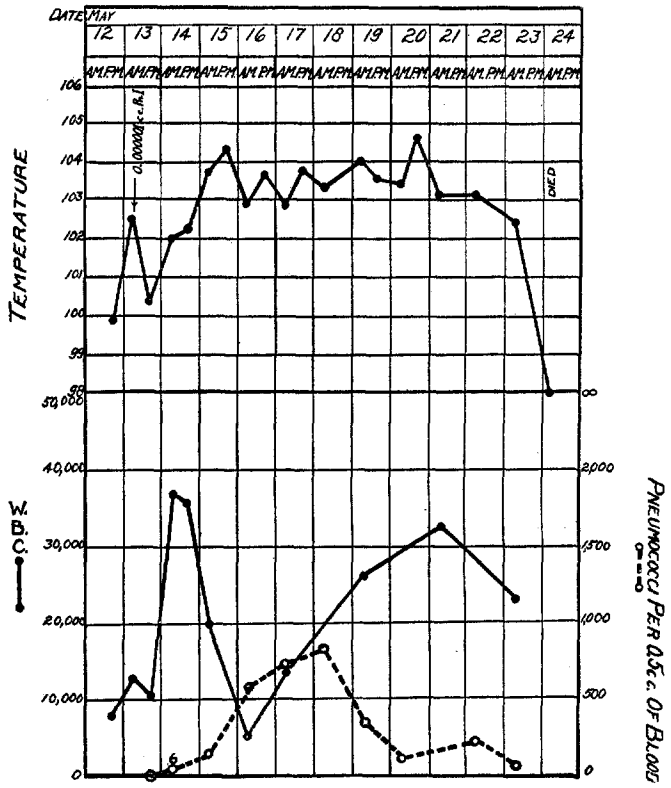
TEXT-FIG. 10. Monkey 31. Experimental lobar pneumonia complicated by empyema following the intratracheal injection of 0.01 cc. of Pneumococcus Type I broth culture.

Experiment 11. Monkey 80 (Text-Fig. 11).—Macacus syrichtus, female; weight 2,850 gm. May 12, 1919. Well and active. May 13, 10.35 a.m. Intratracheal injection of 0.000001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. May 14. Quiet but otherwise appears well. May 15. Sick; respirations rapid and labored. May 16. Condition the same. May 17. Very sick; breathing rapidly. Abdomen distended and tympanitic. Dullness and diminished breath sounds in left lower axilla. May 18 to 22. Condition the same. May 23. Appears better. May 24. Very sick; lying on floor of cage; respirations rapid and gasping. 11.20 a.m. Died.

Autopsy.—Lobar pneumonia, left lower and middle lobes; gray hepatization; acute fibrinopurulent pericarditis; acute fibrinous pleuritis, left.

Cultures.—Heart's blood, pericardial fluid, left lower lobe, Pneumococcus Type I.

Monkey 80 represents a case of lobar pneumonia complicated by a pneumococcus pericarditis. The persisting septicemia with increasing leucocytosis during the latter part of the disease is well shown as in the case of Monkey 31.

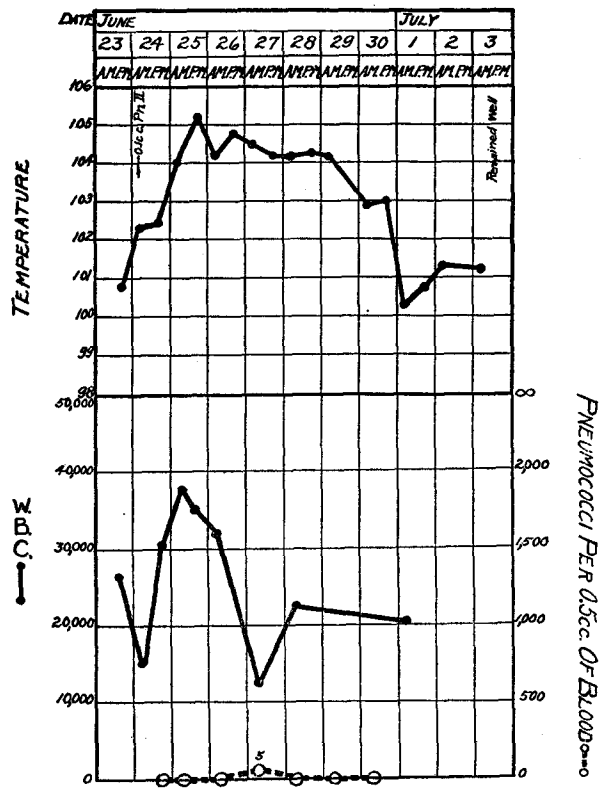


TEXT-FIG. 11. Monkey 80. Experimental lobar pneumonia complicated by fibrinopurulent pericarditis following the intratracheal injection of 0.000001 cc. of Pneumococcus Type I broth culture.

Experiment 12. Monkey 48 (Text-Fig. 12).—Macacus syrichtus, male; weight 3,590 gm. June 23, 1919. Well and active. June 24, 9.55 a.m. Intratracheal injection of 0.1 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type II. June 25. Quiet; breathing moderately accelerated. June 26. Sick; refuses food; breathing rapidly; coughs occasionally. June 27 to 29. Condition the same. June 30. Appears better; more active. July 1. Temperature fallen by crisis. Appears well and active. July 9. Continues well.

Diagnosis.—Lobar pneumonia.

Monkey 48 presents the typical picture of a mild lobar pneumonia caused by Pneumococcus Type II and is analogous in all respects to similar cases produced by the intratracheal injection of Pneumococcus Type I.

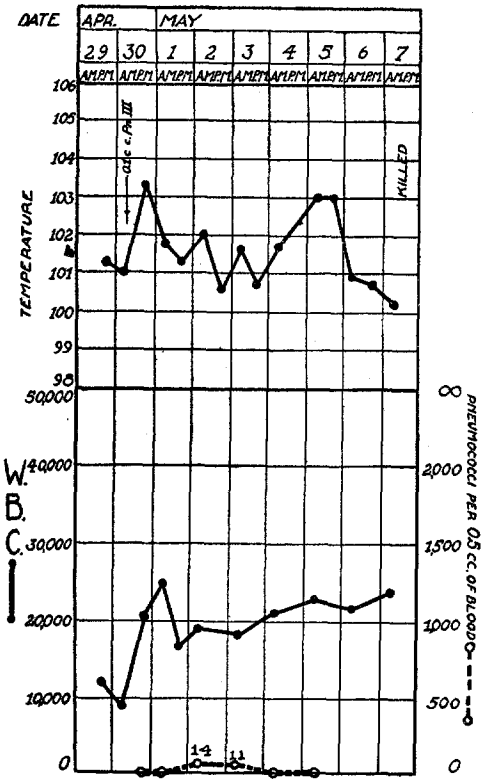


TEXT-FIG. 12. Monkey 48. Experimental lobar pneumonia following the intratracheal injection of 0.1 cc. of Pneumococcus Type II broth culture.

Experiment 13. Monkey 82 (Text-Fig. 13).—Cebus capucinus, male; weight 730 gm. Apr. 29, 1919. Well and active. Apr. 30, 10.15 a.m. Intratracheal injection of 0.1 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type III. 4.20 p.m. Appears sick; shivering violently; breathing rapidly. May 1. Sick; sitting quietly in corner of cage. Respirations rapid; abdomen distended; fine moist râles heard in right axilla. May 2 and 3. Condition the same. Moderate dullness, moist râles, and distant bronchial breathing over right upper lobe. X-ray shows moderately increased density in the right upper lobe. May 5. Improving. May 7. Appears well and active. Killed.

Autopsy.—Resolving interstitial pneumonia, right upper lobe.
Cultures.—Heart's blood and trachea, no growth.

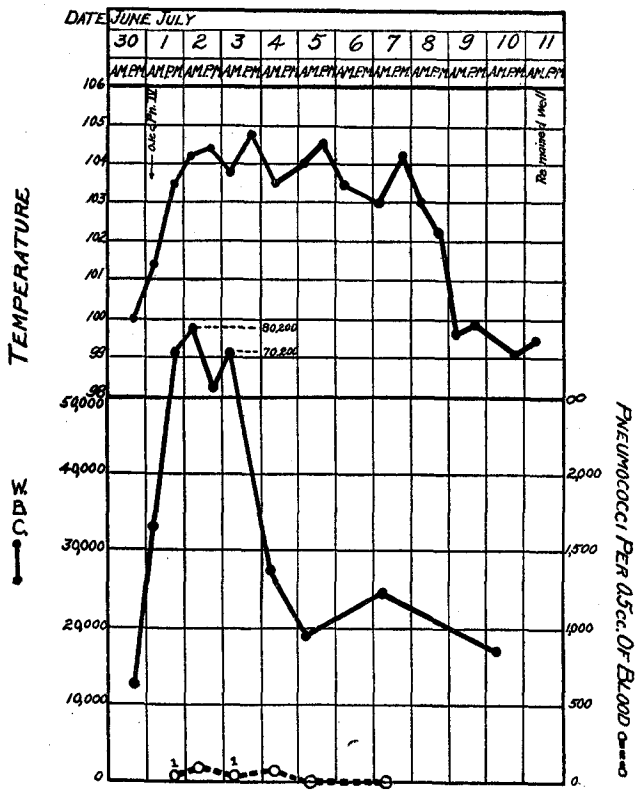
Monkey 82 represents a mild pneumonia due to Pneumococcus Type III. The onset was abrupt, with characteristic chill and sharp elevation in temperature and leucocyte count. The temperature curve, however, was irregular and unusual. It has been stated that



TEXT-FIG. 13. Monkey 82. Experimental pneumonia following the intratracheal injection of 0.1 cc. of Pneumococcus Type III broth culture.

the strain of Pneumococcus Type III used was relatively avirulent for monkeys. This is clearly shown in Monkeys 115 and 107 (Table I) both of which ran short courses of 3 and 4 days duration without invasion of the blood by the pneumococcus. It is probable that similar cases which are occasionally seen in man would be diagnosed as

bronchopneumonia or abortive lobar pneumonia. The latter term would seem preferable, since histological examination has shown that invasion of the lung in these monkeys is identical with the mode of invasion in experimental lobar pneumonia, but that further extension of the process to the stage of alveolar exudation and complete lobar consolidation is checked, presumably because of the resistance of the animal against infection with this strain of pneumococcus. This point is discussed further in Paper II.



TEXT-FIG. 14. Monkey 115. Experimental lobar pneumonia following the intratracheal injection of 0.1 cc. of Pneumococcus Type IV broth culture.

Experiment 14. Monkey 115 (Text-Fig. 14).—Macacus syrichtus, female; weight 3,015 gm. Previously inoculated with Pneumococcus Type III on June 24, 1919. June 30. Well and active. July 1, 11 a.m. Intratracheal injection of 0.1 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type IV. July 2.

Moderately sick; breathing rapidly. July 3. Sick; no appetite; respirations labored and rapid. July 4 to 8. Condition the same. Coughs occasionally. July 9. Appears well and active. Temperature fallen to normal by crisis. July 16. Continues well.

Diagnosis.—Lobar pneumonia.

Monkey 115 shows that the disease produced by the intratracheal injection of Pneumococcus Type IV is identical with that produced by the other types of pneumococci.

Production of Lobar Pneumonia by Contact Infection.

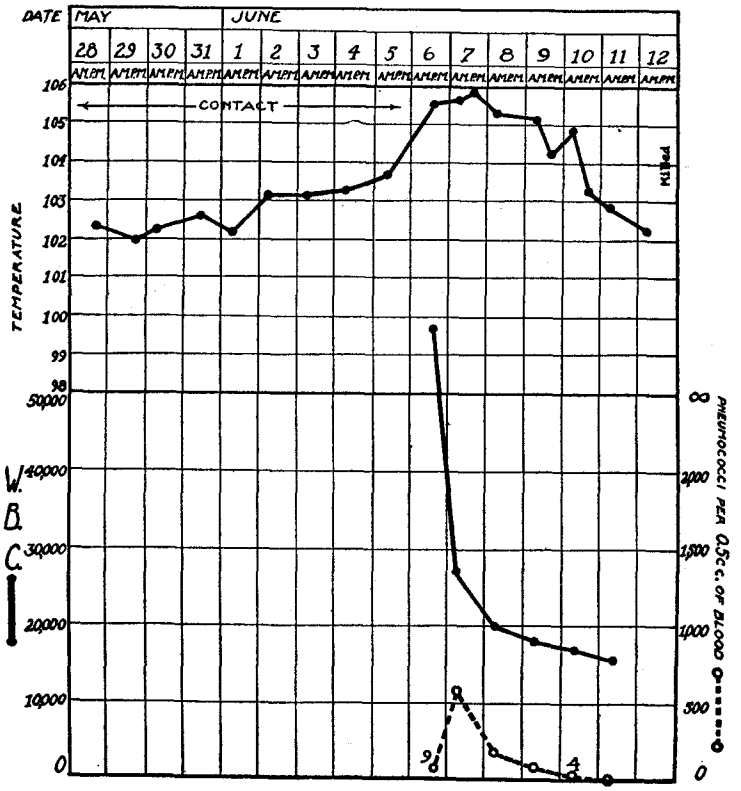
Epidemiological studies by Stillman[4] have clearly indicated that lobar pneumonia in man caused by Pneumococcus Types I and II is probably due in large part to direct or indirect contact infection with other cases of pneumonia caused by these organisms. It was therefore decided to determine whether lobar pneumonia could be experimentally produced in monkeys by contact infection.

Experiment 15.—May 26, 1919. Monkeys 16, 19, 20, 106, 107, and 108 (*Macacus syrichtus*), all well and active, placed in a cage 4 feet by 4 feet by 3 feet. May 27, 10 a.m. Monkeys 109 and 110 (*Macacus syrichtus*) injected intratracheally with 0.001 and 0.000001 cc. of 18 hour broth culture of Pneumococcus Type I, respectively, and placed in the same cage. May 28. Monkeys 109 and 110 have developed pneumonia. Contacts appear well. May 30. Contacts remain well. Monkey 109 died. June 1. Monkey 19 has developed spontaneous lobar pneumonia, Pneumococcus Type IV; removed from cage.[5] Other contacts remain well. June 3. Monkey 110 died. Contacts remain well. June 5. Monkey 112 (*Macacus syrichtus*) injected intratracheally with 0.01 cc. of an 18 hour broth culture of Pneumococcus Type I, and placed in cage. Contacts remain well. June 6. Monkey 112 has developed pneumonia. 3.45 p.m. Contact Monkey 16 appears sick; breathing rapidly. White blood corpuscles 59,700; blood culture shows Pneumococcus Type I (Text-fig. 15). Other contacts well. June 7. Monkey 16 sick; respirations rapid and labored. June 8 to 10. Monkey 16 running typical course of lobar pneumonia. Other contacts remain well. June 10. Monkey 112 died. June 11. Monkey 16 recovered. June 12. Monkey 16 killed. *Autopsy.*—Lobar pneumonia, right lower lobe, resolving. June 20. Contacts remain well. Monkey 114 (*Macacus syrichtus*) injected intratracheally with 0.000001 cc. of an 18 hour broth culture of Pneumococcus Type I, and placed in cage. Developed pneumonia and died on June 25. June 26. Contacts remain well.

[4] Stillman, E. G., *J. Exp. Med.*, 1916, xxiv, 651; 1917, xxvi, 513.

[5] See Paper III (in press).

The production of lobar pneumonia in Monkey 16 by contact infection eliminated the one minor artificial procedure resorted to in the preceding experiments; namely, the introduction of a needle into the trachea. The fact that only one of the six monkeys exposed contracted Pneumococcus Type I pneumonia indicates clearly that



TEXT-FIG. 15. Monkey 16. Spontaneous Pneumococcus Type I lobar pneumonia following contact with cases of experimental Pneumococcus Type I pneumonia.

other factors besides contact play a part in determining whether or not pneumonia will develop. In contrast with this result the constancy with which lobar pneumonia was produced by the intratracheal injection of even very minute amounts of pneumococcus culture clearly indicates that a virulent pneumococcus once having gained entrance to the respiratory tract below the larynx readily produces pneu-

monia in susceptible individuals. Study of the pathogenesis of experimental lobar pneumonia presented in Paper II indicates that it must penetrate as far as the larger bronchi within the lung before pneumonia will develop. The factors which determine whether or not a pneumococcus will gain access to the lower respiratory tract have not been studied. The following experiment clearly shows that its mere presence in the upper respiratory tract even over considerable periods of time is not sufficient in itself to cause even a highly susceptible animal to develop pneumonia.

Effect of Inoculating Monkeys in the Nose and Throat with Virulent Pneumococcus.

Experiment 16.—June 26, 1919. Monkeys 20, 106, 107, and 108 (*Macacus syrichtus*). All well and active. 10.20 a.m. Nose and throat of each monkey sprayed with 2 to 4 cc. of an 18 hour broth culture of Pneumococcus Type I. Monkeys 20, 106, and 108 were held under observation until July 28, Monkey 107 until July 1. All remained perfectly well throughout this period, showing no evidence of pneumonia or of infection of the upper respiratory tract. From time to time saliva was collected and injected intraperitoneally into white mice to determine whether or not Pneumococcus Type I was still present. The results are shown in Table II.

TABLE II.

Persistence of Pneumococcus in the Mouth of Normal Monkeys.

Monkey No.	Date of inoculation.	Pneumococcus Type I in mouth.			
		June 30.	July 7.	July 18.	July 28.
	1919				
20	June 26	+	+	+	+
106	" 26	+	+	+	+
107	" 26	+			
108	" 26	+	+	−	+

The continued existence of a virulent Pneumococcus Type I in the mouths of monkeys for a period of a month without any of them contracting pneumonia is of interest. In connection with experiments with *Bacillus influenzæ* reported in Paper IX it seems advisable to call attention at this point to the fact that a highly virulent pneumococcus inoculated in large amounts into the nose and mouth of animals highly susceptible to pneumococcus infection had absolutely no effect upon them whatsoever.

TABLE III.

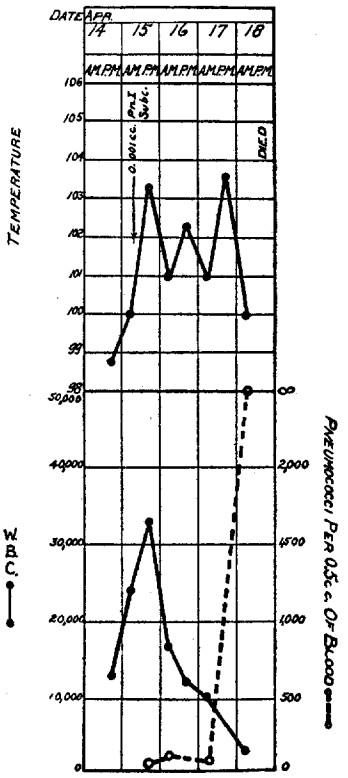
Effect of Intravenous and Subcutaneous Inoculation of Monkeys with Pneumococcus Type I.

Monkey No.	Species.	Weight.	Date of inoculation.	Route of inoculation.	Amount of culture.	Result.	Autopsy.
		gm.	*1919*		*cc.*		
7	*C. capucinus.*	1,430	Mar. 7	Subcutaneous.	0.001	Pneumococcus septicemia. No evidence of pneumonia. X-ray negative. Mar. 14. Recovered.	No autopsy.
46	*M. syrichtus.*	2,550	Apr. 15	"	0.001	Pneumococcus septicemia. Apr. 18. Died.	Pneumococcus septicemia. Lungs normal.
47	" "	2,710	" 15	"	0.001	Temporary febrile reaction and leucocytosis of 24 hrs. duration. Blood sterile.	No autopsy.
48	" "	3,590	" 15	"	0.001	Temporary leucocytosis. No other apparent effect.	" "
8	*C. capucinus.*	1,065	Mar. 7	Intravenous.	0.01	Pneumococcus septicemia. Mar. 8. Died.	Pneumococcus septicemia. Lungs normal.
49	*M. syrichtus.*	4,120	Apr. 15	"	0.001	Pneumococcus septicemia. Apr. 22. Died.	Pneumococcus septicemia. Lungs normal.
104*	" "	1,735	July 8	"	0.001	Temporary pneumococcus septicemia. July 11. Recovered. July 14. Killed.	No lesions.
105*	" "	1,375	" 8	"	0.001	Temporary leucocytosis. No other apparent effect. July 12. Killed.	" "
116	" "	1,935	" 8	"	0.001	Pneumococcus septicemia. No evidence of pneumonia. July 14. Recovered. July 15. Killed.	" "

* Vaccinated with 1 cc. of Pneumococcus Type I saline vaccine (1,000,000,000 pneumococci) on May 22, 29, and June 5, respectively.

Effect of Intravenous and Subcutaneous Inoculation of Monkeys with Virulent Pneumococcus.

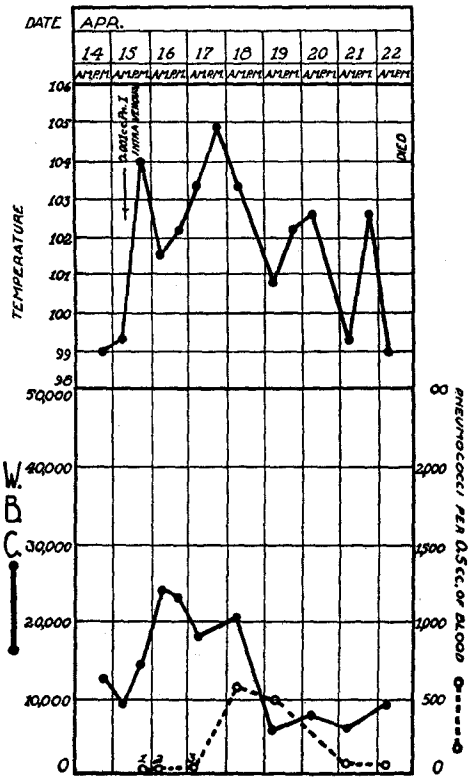
Previous attempts to produce lobar pneumonia in normal animals by intravenous or subcutaneous inoculation of pneumococcus have met with consistent failure.[3] In spite of this fact the theory that the



TEXT-FIG. 16. Monkey 46. Effect of the subcutaneous injection of 0.001 cc. of Pneumococcus Type I broth culture.

disease in man is hematogenous rather than bronchiogenic in origin has from time to time been advanced, although without convincing evidence to support it. It therefore seemed advisable to control the results obtained by intratracheal injection by a series of experiments to determine the effect of intravenous and subcutaneous inoculation of pneumococcus in monkeys. Five monkeys received intravenous in-

jections and four monkeys subcutaneous injections of 0.01 to 0.001 cc. of an 18 hour broth culture of Pneumococcus Type I, the same strain being used as in the preceding experiments, all with entirely negative results in as far as the production of pneumonia was concerned. The results are shown in Table III. Individual variation in susceptibility probably explains the different results obtained.



TEXT-FIG. 17. Monkey 49. Effect of the intravenous injection of 0.001 cc. of Pneumococcus Type I broth culture.

Two illustrative protocols with accompanying clinical charts are presented.

Experiment 17. Monkey 46 (Text-Fig. 16).—Macacus syrichtus, female; weight 2,550 gm. Apr. 14, 1919. Well and active. Apr. 15, 10 a.m. Subcutaneous injection of 0.001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus

Type I. Apr. 16. Quiet but otherwise appears well. Apr. 17. Appears moderately sick; breathing normally; chest clear. Apr. 18. Sick; respirations slow; chest clear; abdomen slightly distended. Apr. 19. Found dead in morning.

Autopsy.—No lesions; lungs normal; pneumococcus septicemia.

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

Experiment 18. Monkey 49 (Text-Fig. 17).—Macacus syrichtus, male; weight 4,120 gm. Apr. 14, 1919. Well and active. Apr. 15, 10.30 a.m. Intravenous injection of 0.001 cc. (in 1 cc.) of 18 hour broth culture of Pneumococcus Type I. Apr. 16. Quiet; respirations normal; chest clear. Apr. 18. Moderately sick; no definite symptoms; chest clear. Apr. 19 to 21. Condition the same. Apr. 22. 1 p.m. Very sick; lying on floor of cage. 3 p.m. Died.

Autopsy.—No lesions; lungs normal; pneumococcus septicemia.

Culture.—Heart's blood, Pneumococcus Type I.

Monkeys 46 and 49 show that pneumococci injected subcutaneously or intravenously exhibit no tendency to localize in the lungs, or, in fact, anywhere in the body, but produce only a pneumococcus septicemia. Symptoms characteristic of lobar pneumonia were entirely lacking in both animals throughout the course of the infection as they have been in other animals so inoculated.

Effect of Intratracheal Injection of Sterile Broth, Killed Pneumococcus Culture, and Living Avirulent Pneumococcus.

A few further experiments to control the results obtained by intratracheal injection of living virulent pneumococci were carried out as shown in Table IV.

The entirely negative results in these experiments show that the direct intratracheal injection of 1 cc. of fluid with or without pneumococcus cells was not in itself in any way responsible for the development of pneumonia in monkeys injected by this method with living virulent pneumococci.

TABLE IV.

Effect of Intratracheal Injection of Sterile Broth, Killed Pneumococcus Culture, and Living Avirulent Pneumococcus.

Monkey No.	Species.	Weight.	Date of injection.	Material injected.	Result.	Autopsy.
		gm.	*1919*			
5	*C. capucinus.*	1,410	Feb. 28	1 cc. of sterile broth.	Slight polymorphonuclear leucocytosis 6 hrs. after injection. No other effect.	No autopsy.
10	" "	827	Mar. 18, 10.45 a.m.	1 cc. of Pneumococcus Type I broth culture previously killed by heating at 55°C. for 45 min.	Slight febrile reaction 6 hrs. after injection. Moderate polymorphonuclear leucocytosis 6 hrs. after injection. No other effect. Mar. 19, 3 p.m. Killed.	Lungs appear normal. Microscopic examination shows no abnormalities.
24	" "	855	Mar. 20, 10.15 a.m.	2 cc. of 18 hr. broth culture of avirulent strain of Pneumococcus Type I.	No febrile reaction. Blood sterile. Moderate polymorphonuclear leucocytosis 6 hrs. after injection. Mar. 21. X-ray of chest negative. Remained well.	No autopsy.

DISCUSSION.

That the disease experimentally produced in monkeys by the intratracheal injection of minute amounts of pneumococcus cultures is clinically identical with lobar pneumonia in man seems quite clear and requires no special comment. Certain features of the disease, however, which have come out during the course of the study require discussion, since they may serve to throw some light on the course of lobar pneumonia in man.

Although it is generally believed that lobar pneumonia is bronchiogenic in origin there has been no certain evidence that such is the case, as the recurring suggestion that it may be hematogenous in origin testifies. The latter conception has apparently depended upon the clinical observation of cases in which the pneumococcus was shown to be present in the blood at the time of onset of clinical symptoms of pneumonia, or in occasional instances before the clinical symptoms of pneumonia had appeared. That the interpretation of this observation as indicative of the hematogenous origin of lobar pneumonia is incorrect is established by the fact that in the majority of instances in pneumonia experimentally produced by the intratracheal injection of pneumococcus, the organisms have appeared in the blood stream within from 6 to 24 hours after injection, frequently before clinical evidence of pneumonia or elevation of temperature had developed. It is presumable that they rapidly gain access to the blood by way of the lymphatics draining from the lungs, a supposition well supported by histological study of the earliest stages of experimental pneumonia presented in the following paper. The constant production of the disease by intratracheal injection and the constant failure to produce it by other methods of inoculation are believed to be conclusive evidence that infection in lobar pneumonia takes place by way of the respiratory passages.

The failure to produce pneumonia by the instillation of large amounts of a virulent pneumococcus culture into the nose and throat of animals as highly susceptible to pneumococcus infection as monkeys, even though the animals so inoculated continued to carry the pneumococcus in the mouth for at least a month, clearly suggests that there are unknown factors which determine whether or not a

virulent pneumococcus in the upper respiratory tract will gain access to the bronchi. No experiments to determine what these factors are were carried out. It seems established by this observation, however, that the pneumococcus is incapable of initiating an infection of the normal upper respiratory tract in monkeys at least, and that it should probably be regarded only as a secondary invader when found associated with such infections in man.

It is generally stated that the degree of leucocytosis in lobar pneumonia in man is inversely proportional to the severity of the pneumonia, but that individual variation is so great that it is of little prognostic value in the given case. Analysis of the leucocytic reaction during the course of the disease in monkeys, however, has shown a rather surprising constancy in the relation between the leucocyte curve and the severity of the infection as measured by the degree of septicemia, the development of complications, and the final outcome. It has been stated that the onset of pneumonia in monkeys is accompanied by an initial leucocytosis. This preliminary leucocytosis, which was polymorphonuclear in character, usually began within 6 hours after injection and reached its apex within 24 to 48 hours. It varied from 35,000 to 90,000 cells per c.mm., the polymorphonuclear neutrophils comprising from 85 to 95 per cent of the leucocytes. It was not possible to establish any apparent relation between the height of this leucocytosis and the subsequent course of the disease. It was well developed in many cases before clinical evidence of pneumonia or elevation of temperature had occurred, in this respect being similar to the frequent early invasion of the blood by pneumococci. There seems little doubt that it occurred as an immediate response on the part of the animal to invasion of the pulmonary tissue by the pneumococcus and represents an effort on the part of the host to combat the infection at the point of entrance. This was shown to be the case in a monkey killed 3 hours after intratracheal injection (Monkey 72, Paper II), the leucocytes having increased from 15,200 per c.mm. to 25,700 per c.mm. in that time. Histological sections of the right lower lobe showed extensive infiltration of polymorphonuclear leucocytes in the peribronchial tissue near the hilum, many leucocytes passing through the mucosa of the bronchial wall, and many already extruded into the lumen of the bronchus. A

similar though more extensive infiltration of leucocytes was observed in several monkeys dying within 48 hours after inoculation. In some of these considerable phagocytosis of pneumococci had already taken place.

Following the preliminary rise in leucocytes there has been a constant fall in the curve. The rapidity and extent of this fall has seemed to bear a direct relation to the severity of the disease and the degree of pneumococcus invasion of the blood. This is clearly illustrated by contrasting the leucocyte curve of Monkey 115 (Text-fig. 1) with that of Monkey 110 (Text-fig. 5). Study of stained blood films has shown that during this fall mature polymorphonuclear leucocytes are increasingly replaced by young forms with two or three nuclear lobules, until in the very severe cases with overwhelming septicemia and marked leucopenia mature leucocytes have practically disappeared from the blood. In the latter group of cases occasional nucleated red blood corpuscles, myelocytes, and polychromatophilic cells simultaneously appear. This phenomenon points to an initial intense stimulation of the bone marrow followed by a progressive exhaustion as the severity of the infection increases. In harmony with this supposition is the observation that the bone marrow of monkeys dying early with an overwhelming septicemia has frequently been almost entirely devoid of polymorphonuclear leucocytes, and myelocytes have been few in number. It would appear that the leucocytes available at the onset of the disease are transported bodily, so to speak, from the bone marrow to the lungs and that the animal is no longer able to respond with further production of leucocytes in the presence of an overwhelming infection. Whether the progressive exhaustion of bone marrow activity is due to the increasing severity of the infection, or the increasing severity of the infection is due to an inherent weakness of the leucocytic defense in the individual animal is uncertain.

In contrast with the foregoing picture is the one presented by less severe cases which progress favorably to recovery. The leucocyte curve instead of continuing progressively downward turns upward again and progressively rises during the latter half of the disease until crisis occurs, when it again falls to normal. Simultaneously with this increase in leucocytes, the degree of septicemia diminishes until the

blood becomes sterile, usually several days before crisis. This phenomenon has been surprisingly constant and has occurred in nearly all the cases that have recovered. It has been pointed out that a few animals exhibiting this secondary rise in the leucocyte curve have shown a continuing septicemia which terminated in death. In this small group of cases autopsy has shown a complicating pericarditis or empyema in most instances. In both these groups the bone marrow has frequently shown greatly increased numbers of myelocytes.

The mechanism of recovery from lobar pneumonia has been the subject of much investigation. Neufeld and Haendel, Cole and his coworkers, Blake, and others[6] have attributed it in part to the development of humoral antibodies and have demonstrated the appearance of these antibodies in the circulating blood at or about the time of crisis. More recently Lord[7] has suggested that another factor may be of considerable importance in bringing about crisis and resolution of the pneumonic process, attributing recovery to local biochemical changes in the course of which the acid death-point of the pneumococcus is reached. Although no study of the mechanism of crisis has been made in the course of the experiments reported, certain isolated observations seem of interest in this connection. In one instance crisis with recovery occurred with pneumococcus septicemia persisting for 48 hours after crisis. In several instances a critical fall in temperature has occurred about the 7th to 9th day with subsequent return of fever and death several days later. Autopsy has shown a resolving pneumonia, death apparently being due to a persisting pneumococcus septicemia usually associated with some complication. In another small group of cases recovery from the general pneumococcus infection has occurred as evidenced by the disappearance of pneumococci from the blood. Crisis, however, did not occur and the monkeys finally died showing an unresolved pneu-

[6] Neufeld, F., and Haendel, *Arb. k. Gsndhtsamte.*, 1910, xxxiv, 166. Dochez, A. R., *J. Exp. Med.*, 1912, xvi, 665. Avery, O. T., Chickering, H. T., Cole, R., and Dochez, A. R., Acute lobar pneumonia. Prevention and serum treatment, Monograph of The Rockefeller Institute for Medical Research, No. 7, New York, 1917. Blake, F. G., *Arch. Int. Med.*, 1918, xxi, 779.

[7] Lord, F. T., *J. Exp. Med.*, 1919, xxx, 379.

monia with pneumococci still present in the lung. These observations, though far from proving the fact, are not out of harmony with the theory advanced by Lord with respect to the mechanism of crisis and suggest that other important factors besides the development of humoral immunity are necessary to bring about recovery from pneumonia. With these points in mind it does not seem unreasonable to look upon lobar pneumonia as comprised of two distinct though intimately related processes; one, always present, being the local pulmonary lesion, the other, present in a variable number of cases, being a general infection of the body as manifested by the frequent pneumococcus septicemia. Though ultimate recovery must primarily depend upon the ability of the individual to prevent or terminate the general infection when once established, presumably through the existence or development of a humoral immunity, it does not follow that recovery from the local process with resolution of the pneumonic consolidation need be either coincident with recovery from the general infection or dependent upon the same mechanism. In fact, it would seem well established by numerous clinical observations that recovery from the general pneumococcus infection when it exists usually precedes, by several days at least, recovery from the disease at the time of crisis. On the other hand, certain of the observations cited above would seem to indicate that recovery from the local process as shown by a rapidly resolving pneumonia may occasionally occur prior to recovery from the general infection or even when death from the general infection subsequently takes place. In view of the above considerations it would seem not improbable that at least a dual mechanism may be concerned in bringing about final recovery from lobar pneumonia. Expression of any certain opinion on the subject, however, must depend on much further work.

SUMMARY.

1. Lobar pneumonia has been consistently produced in normal monkeys by the intratracheal injection of minute amounts of pneumococcus culture.

2. The disease produced has been shown to be clinically identical with lobar pneumonia in man.

3. Lobar pneumonia has been produced in the monkey in one instance by experimental contact infection.

4. Normal monkeys inoculated in the nose and throat with large amounts of pneumococcus culture have failed to develop lobar pneumonia though carrying the organism in their mouths for at least a month. They have likewise failed to show any evidence of upper respiratory tract infection.

5. Monkeys inoculated subcutaneously or intravenously with pneumococcus culture have in no instance developed pneumonia, but have either died of pneumococcus septicemia or recovered without localization of the infection in the lungs.

CONCLUSIONS.

1. The pneumococcus is the specific cause of lobar pneumonia.

2. The pneumococcus is unable to initiate an infection of the normal mucous membranes of the upper respiratory tract or to produce pneumonia following intravenous injection, but must gain access to the lower respiratory tract by way of the trachea in order to cause pneumonia.

3. Lobar pneumonia is, therefore, bronchiogenic in origin.

4. Invasion of the blood stream by the pneumococcus in lobar pneumonia is secondary to infection of the lungs.

5. The character of the leucocyte reaction during the course of lobar pneumonia bears a fairly definite relation to the course of the disease.

EXPLANATION OF PLATE 21.

FIG. 1. Monkey 75. Experimental lobar pneumonia; Pneumococcus Type I. X-ray of the chest showing consolidation of the left lower lobe.

FIG. 2. Monkey 3. Experimental lobar pneumonia; Pneumococcus Type I. X-ray of the chest showing consolidation of the left upper lobe.

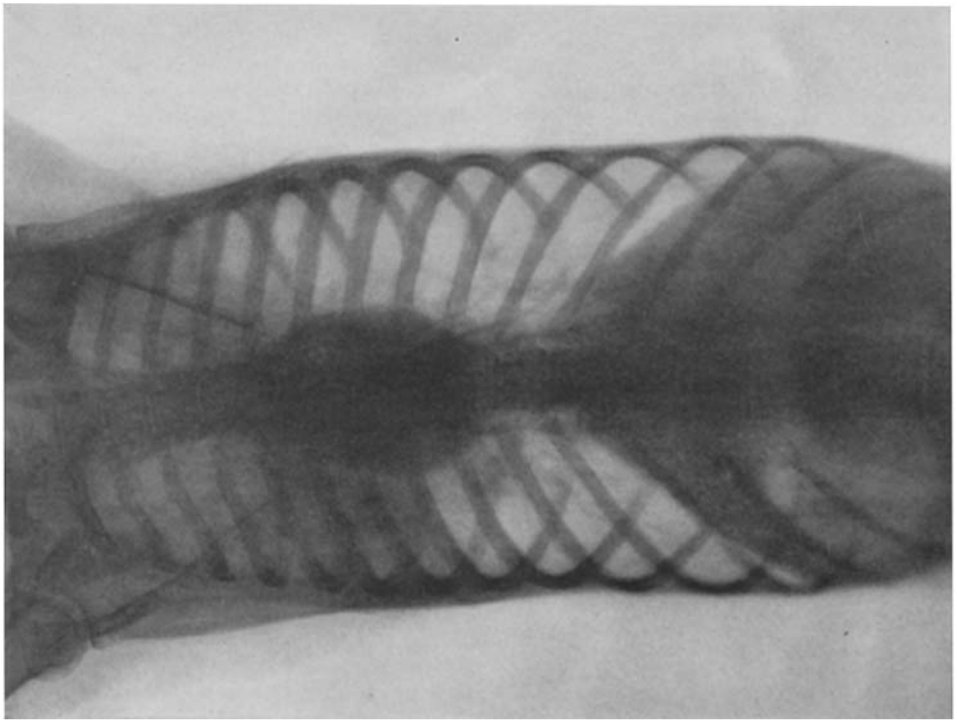


FIG. 2.

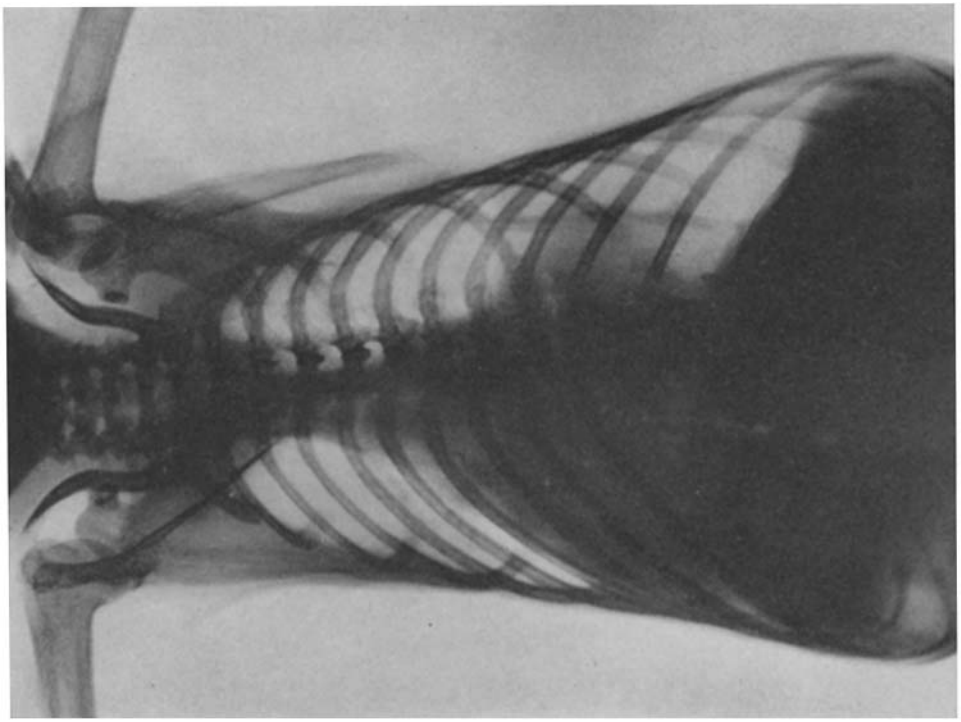


FIG. 1.

(Blake and Cecil: Experimental pneumonia. I.)