EXPERIMENTAL PNEUMONIA BY INTRABRONCHIAL INSUFFLATION.*

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INTRODUCTION.

The most reliable evidence of an etiological relationship between a given microörganism and a definite disease is the experimental production of the disease by a pure culture of the microörganism. It is a quarter of a century since the organism which is now generally termed pneumococcus was brought into etiological connection with lobar pneumonia, and it is now generally accepted that this disease is, in most cases, caused by an infection of the lungs with the pneumococcus. Nevertheless, this assumption rests essentially on the statistical evidence that in most cases of lobar pneumonia the pneumococcus is recoverable from the lungs of the patients; while the more convincing evidence based upon the experimental production of pneumonia by inoculations with pure cultures is, in spite of numerous experiments, still lacking. If we are to judge from text-book and other statements, this fact is not generally appreciated. We shall therefore try to bring it out by a brief analysis of the data contained in the literature.[1]

We can omit the numerous experiments made in various ways with pure and impure cultures of the pneumococcus, the purpose of which was to ascertain the pathogenicity, and which led in most instances to septicemia, and only incidentally and exceptionally set up at the same time a pneumonia. We shall restrict our reference to those experiments that had as their exclusive object the production of pneumonia. Three methods of introduction of the pure cultures of the pneumococcus into the lungs were employed for this purpose: direct injection

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* Received for publication, December 16, 1911.

[1] A recent paper by Wadsworth, entitled "Experimental Studies on the Etiology of Acute Pneumonitis" (*Am. Jour. Med. Sc.*, 1904, cxxvii, 851), contains a review of the literature and a bibliography of 198 references.

of the culture into the lung tissue through the thoracic wall, intratracheal injection, and inhalation of the culture. The failure of the last named method is generally admitted, although several investigators believed that an occasional positive result was obtained. It is different with the other two methods. Gamaléia[2] reported that by injection of pneumococcus cultures through the chest wall directly into the lungs of dogs and sheep he obtained constantly pneumonic lesions, and Tchistovitch[3] stated that by intratracheal injections of cultures into dogs he succeeded in seven out of nineteen experiments, while Monti[4] claimed to have obtained constantly positive results by intratracheal injections in rabbits. These are the statements that are chiefly before the minds of those writers who consider that the experimental proof of the causation of pneumonia by the pneumococcus has been rendered. As a matter of fact, the several claims mentioned were put forward in the early years after the etiological connection of the pneumococcus with pneumonia had been expounded by Fränkel, but they were not substantiated by any subsequent experimenters. Kruse and Pansini,[5] who dismiss the experiments of Monti as insufficiently described and untrustworthy, failed to confirm the experiments of Gamaléia. Referring to the experiments of Gamaléia, Welch[6] says: " They are not described with sufficient detail to permit critical judgment, nor have they been satisfactorily confirmed by other investigators. Many inoculations of cultures of virulent pneumococci into the trachea and lungs of dogs have been made in my laboratory by Dr. Canfield and myself, but in no instance were we able to produce an inflammation of the lungs which we were willing to identify with acute lobar pneumonia as found in human beings. In the majority of our experiments there was no appreciable effect." Welch states further: " The domestic animals are not subject to a form of pneumonia etiologically and anatomically identical with croupous pneumonia of man. Bacteriologists are not always pathologists and the bare statement that the pneumonia produced experimentally is in all respects identical with acute lobar pneumonia in human beings should be received with caution." With the exception of that of Wadsworth, in the intervening nineteen years no investigation embodying a larger measure of success in the production of pneumonia in animals has appeared. This failure was, however, not utilized as proof against the claim that the pneumococcus is the cause of lobar pneumonia in man. Indeed, the failure to produce successfully the disease in animals was explained either by the assumption that the experimental animals employed are not susceptible to exactly this form of disease; or that besides the presence of the pneumococcus in the lungs there must coëxist other factors in the host that are indispensable for the development of the typical form of lobar pneumonia. The latter hypothetical notion was tested in several series of experiments which need not here be dwelt upon. It suffices to state that no well defined condition has thus far been discovered with the aid of which it is possible, using any

[2] Gamaléia, *Ann. de l'Inst. Pasteur,* 1888, ii, 440.

[3] Tchistovitch, *Ann. de l'Inst. Pasteur,* 1890, iii, 285.

[4] Monti, after Kruse and Pansini (see reference 5).

[5] Kruse and Pansini, *Ztschr. f. Hyg. u. Infectionskrankh.,* 1892, xi, 337.

[6] Welch, *Bull. Johns Hopkins Hosp.,* 1892, iii, 125.

method of inoculation, to produce in animals, with fair constancy, definite lobar pneumonia. The assumption that experimental animals are not subject to lobar pneumonia is based upon the idea that some animals are so highly susceptible to the infective action of the pneumococcus that an inoculation of the lungs leads to a fatal septicemia without causing any local reaction in the lungs; while others are equally refractory to infection, perhaps by reason of the capability of the tissues of their lungs to destroy the invading organisms without the aid of any inflammatory reaction whatever. This conception was the starting point that enabled Wadsworth[7] to develop a method by which he succeeded in producing pneumonia successively in eleven rabbits. Rabbits are highly susceptible to the action of the pneumococcus, and the inoculation into the lungs of virulent cultures leads to a fatal septicemia without causing pneumonia. Wadsworth reduced experimentally this susceptibility by previously immunizing, in some degree, the rabbits, after which he injected pure cultures of pneumococcus of moderate virulence intratracheally. The positive outcome of the experiment would appear to depend upon an exact adjustment between the virulence of the micröorganism and the susceptibility of the animal—a condition difficult to control. Although Wadsworth's experiments were reported about eight years ago, they appear not to have been repeated and confirmed.

In a preliminary note,[8] we reported upon our efforts to produce pneumonia in dogs by injecting cultures of the pneumococcus through the trachea into the bronchi, and pointed out that there may be produced regularly in this manner an extensive, evenly distributed, fibrinous pneumonia affecting the whole, or almost the whole, of one lobe or even two or more lobes of the lungs. The experiments were continued, and the present paper contains a more detailed report of the results achieved, as well as a consideration of their significance.

EXPERIMENTAL DATA.

Methods.—All the experiments were made upon dogs. The method consists in injecting pure cultures of the pneumococcus or other organisms into the lungs through a catheter or small stomach tube which is introduced through the mouth, larynx, and trachea into a bronchus by the insufflation procedure of Meltzer and Auer.[9]

The procedure is as follows: In a deeply etherized dog the mouth is kept wide open by means of a large wooden gag, the tongue is pulled out by means of hemostatic forceps, and then the median glosso-epiglottic frenum is grasped with a curved forceps and gently pulled forward. The now clearly visible pos-

[7] Wadsworth, *loc. cit.*

[8] Lamar and Meltzer, *Proc. Soc. Exper. Biol. and Med.,* 1909–10, vii, 102.

[9] Meltzer, *Med. Rec.,* 1910, lxxvii, 477; *Jour. Am. Med. Assn.,* 1911, lvii, 521.

terior aspect of the epiglottis presents an inclined plane into the concavity of which one end of the tube is placed. Under the protection of the left index finger the tube is now directed into the larynx and pushed down slowly and gently through the trachea until a resistance is met with. The inner end of the tube is now in a bronchus, and usually in the right bronchus. The smaller the diameter of the tube, the deeper it enters into the bronchi. The opening of the tube should be at the end and not on the side where it usually is in catheters. A pipette containing the liquid culture is now attached to the external end of the tube, and by means of a syringe attached to the pipette the culture is injected into the bronchus. The syringe is now taken off, the piston withdrawn, and the syringe again attached to the pipette. By the injection of air the culture is now driven still deeper into the bronchi. The tube is clamped and withdrawn, and the animal released from the table.

The pneumococcus employed in the experiments was obtained from the sputum of a patient suffering from lobar pneumonia, and it had the characteristics of what is commonly termed a typical pneumococcus,—occurrence in pointed pairs, possession of capsules, solubility in bile, and ability to ferment inulin. Its virulence had been exalted to a high degree and was maintained at a constant level, in so far as one may know from the methods in use, by regular "passage" in mice, for which 0.000,001 of a cubic centimeter was fatal. Plain broth made from beef adjusted to a reaction of $+0.5$ per cent. to $+0.7$ per cent. (phenolphthalein) and sterilized fractionally in live steam was used as the culture medium. In such a broth the pneumococcus grows profusely, preserves its virulence, and suffers a minimum of involution and the autolysis to which it is prone.

The quantity of culture injected varied according to the particular purpose of the individual experiment from 0.5 of a cubic centimeter to 25 cubic centimeters. Most often it was from 5 to 10 cubic centimeters.

Results.—While some of the animals died as a result of the pneumococcus infection, most were killed for anatomical and bacteriological examination of the lungs at varying intervals of time, from one day to several weeks, after the injection was made.

Apparently in accordance with the quantity of culture injected the disease has been mild, of moderate severity and followed by recovery, or very severe and terminated by death. Correspondingly in the one there has been consolidation of nearly all of one lobe of

the lung with a concomitant dry pleurisy, while in the other, there was usually consolidation of more than one lobe, accompanied by empyema, pericarditis, and septicemia. For the sake of convenience and clearness composite type descriptions drawn from the many individual examples of each variety will be given.

Non-Fatal Effects.—In most instances the disease produced was of the milder type. Within a few hours of the injection of the smaller or moderate quantity of culture, the animal eats little or nothing, becomes quiet, and its temperature rises two or three degrees Centigrade. This condition continues for the remainder of the day. On the next day, there is still slight fever, food is still refused, but the animal appears to be better. On the third day, the clinical symptoms have already subsided by lysis, after which there are no further objective signs of illness. Yet, as will be shown later, if the animal is killed at this time, the inflammatory exudate is found to be little diminished, although resolution has begun. Cough was noticed in a few instances only, and merely for a short time after the injection.

This has been the usual course. In a few instances, however, slight fever persisted, or returned after the temperature had been normal for one day or longer. In these cases the anatomical and bacteriological examination revealed a complication due to secondary invasion of the distemper bacillus.

By examining the lungs of the animals that died and of those that were killed at daily intervals from one to twelve days after the injection, it has been possible to follow the character of the consolidation, the changes which take place in the exudate, and the fate of the pneumococci.

In most of the experiments the consolidation was confined to the right lung and usually occurred in the posterior lobe, occasionally in the internal or subcardiac lobes. The anatomical relation of the right bronchus to the trachea explains this selection. Sometimes consolidation existed in the left lung but almost always in association with consolidation in the right lung.

The course of the inflammation in the lung is rapid, and consolidation occurs quickly. Thus seven hours after the injection, which is the earliest observation secured, nearly complete consolidation affecting the greater part of one lobe was already present.

At the end of twenty-four hours nearly the whole of the right posterior lobe is solid and airless except for a small area at the anterior superior angle. Here are found usually only congestion and some edema, the inflammation not progressing to the point of complete consolidation. Often the entire lobe is solid; nearly always when it is the internal one that is affected. Rarely the consolidation is confined to the left posterior lobe, and then, as in the right, the anterior tip is commonly spared. The visceral pleura of the consolidated lobe is dark red and has lost its luster. There is a general deposit of fibrin as fine granules, with here and there a few small flakes or even a fairly large sheet. The consolidated portion is uniformly firm and inelastic, the lobe not flattening from gravity when placed upon the board. Excised portions sink at once in water. The cut surface is dark red, not very moist, and somewhat granular. On firm compression only a moderate quantity of rather thick bloody fluid can be squeezed out, the tissue soon giving way with a ragged line of fracture.

The exudate consists mainly of well preserved polymorphonuclear leucocytes closely filling the alveoli. There are red blood cells free in the alveoli but they are usually relatively few in number and unequally distributed; some alveoli contain many, and others only a few. Occasionally many alveoli are filled with red blood cells. Fibrin is present throughout as fine threads and granules. At this early stage, as is the rule in sections made from inflamed tissue, it is not as prominent or apparently as abundant as a day or two later. The bronchi, themselves free from inflammation, are filled with the exudate from the alveoli. When the whole lobe is not consolidated, the composition of the exudate changes near the site which is only congested and edematous. Here serum begins to predominate over cells, the leucocytes are fewer, and there is some epithelial desquamation.

At this time pneumococci are seen in large numbers, capsulated, in pairs, and often in short chains. They lie extracellularly for the most part, free in the alveoli and finer bronchial vessels. Examples of phagocytosis are not numerous.

The lymph nodes related anatomically to the consolidated lobe are swollen, soft, and moist. The sinus contains many polymorpho-

nuclear cells, and the germinal centers are prominently defined. There is often a mild degree of acute splenic tumor.

By the end of the second day the pleura is more dull and the quantity of fibrin is increased, often to the extent of shaggy patches. The consolidated portion of the lung is still firm, but it already begins to flatten from gravity and is less friable. Some of the polymorphonuclear leucocytes are disintegrating. In a few alveoli there are free large mononuclear cells, some of which have ingested polymorphonuclear leucocytes. Examples of this macrophage activity may be seen also in the vessels of the lymph plexus deep in the pleura.[10] The diplococci are fewer in number and many are now intracellular. Growth from the exudate is not so profuse as before.

On the fourth day, resolution is fairly inaugurated. The lobe is softer and no longer uniform in color and consistence, some parts being softer and of a lighter red color than others, or even grey. Nearly all of the pus cells stain poorly, the ratio of large mononuclear cells has increased, and a fair proportion of alveoli contain only, or largely, serum. Phagocytosis of the polymorphonuclear cells continues to a greater extent. Many examples of it are seen in the alveoli, in the lymph vessels, and in the peripheral sinus of the related lymph nodes, the swelling of which has subsided.

Usually at this time only a few diplococci may be observed, and they lie within the polymorphonuclear cells. Transplantations furnish slight growth.

From now on resolution proceeds rapidly but not uniformly throughout. It advances rather from the edge and circumference of the lobe and the anterior margin of the consolidated part toward the center, where it is slowest about the larger bronchial vessels, and the diaphragmatic surface. Sometimes by the end of the first week little of the exudate remains. Nearly always before two weeks have passed the lung has returned to the normal condition.

In several instances, resolution was not complete, there being left behind one or more small streaks or patches in the thin edges of the

[10] From the constancy of its occurrence and the many examples of it, this phagocytic activity of the large mononuclear cells, to the occurrence and significance of which in inflammation Opie (Harvey Lectures, 1909-1910, 192) has recently again directed attention, seems to be an important factor in the removal of the exudate.

lobe where the persisting exudate was undergoing organization. In two instances, organization of the exudate was extensive, once affecting nearly the entire lobe. It is likely that organization is more or less dependent upon the secondary invasion of the exudate by the distemper bacillus, since in some instances, in the early stages, we have cultivated the bacillus of that affection. Later, as is customary in the spontaneous pneumonia of dogs which is prone to undergo partial organization, no growth is obtained.

ILLUSTRATIVE PROTOCOLS.

Dog 7.—Mongrel, male. Weight, 5.3 kilos.

March 23, 1910. 11 A. M. Temperature 38.6°. 11.30 A. M. Under ether anesthesia, injected intrabronchially 5 c.c. of a 20 hour plain broth culture of pneumococcus N. I. The animal recovers promptly and completely in a few minutes, as from simple anesthesia. 5.00 P. M. Quiet; seems ill; temperature 40.4°.

March 24. 10 A. M. Better, but not normal. Weight, 4.9 kilos. Temperature 38.8°. 11 A. M. Killed with ether.

Autopsy.—Performed at once. The posterior lobe of the right lung is completely consolidated for about four fifths of its extent. The remaining fifth at the anterior superior angle is congested and edematous. The surface of the consolidated portion is raised, dark red, moist, and glistens less than the other lobes of both lungs. Consistence is evenly firm. Excised portions sink at once in water. The cut surface is evenly dark red, very moist, and finely granular. Upon squeezing, there is much thick blood-stained fluid unmixed with air, and the cut bronchial vessels exude a viscid, reddish brown, semifluid material.

On the contiguous inferior surface of the right middle lobe is a thin, dark red streak following, and adjacent to, the main bronchial vessel. It contains air throughout. The remainder of the right lung, as well as the entire left lung, is normal in appearance.

The lymph nodes at the root of the right lung are swollen and soft; in section they are moist and translucent.

Smears of scrapings from the cut surface of the consolidated portion contain a great many well preserved polymorphonuclear leucocytes, a moderate number of red blood cells, a few large mononuclear cells, and a fair number of extracellular, pointed, Gram positive, capsulated diplococci. Smears from the congested and edematous anterior angle of the lobe show much serum, many polymorphonuclear cells, and many diplococci.

Cultures.—From the consolidated portion of the right posterior lobe: profuse growth of pneumococcus; pure.

From an opened bronchial vessel in the same portion: the same.

From the adjacent edematous portion: the same.

From the right middle, right upper, and left lower lobes: no growth.

In sections from the consolidated portion, all of the alveoli are evenly filled with well stained polymorphonuclear leucocytes with a very few red blood cells here and there. At the edge of the consolidated area the alveoli contain fewer and fewer polymorphonuclear cells, more and more serum, and a good number of desquamated epithelial cells.

Dog 5 (New Series).—Weight, 10.5 kilos.

October 7, 1910. 10 A. M. Temperature 38.4°. 11 A. M. Under ether anesthesia, injected intrabronchially 5 c.c. of a 24 hour plain broth culture of pneumococcus N. I. Quick, complete recovery. 5 P. M. Quiet; temperature 39.8°.

October 8. 10 A. M. Temperature 39.5°.

October 10. 10 A. M. Temperature 39.5°.

October 11. 10 A. M. Temperature 39.3°.

October 12. 10 A. M. Temperature 39.5°.

October 13. 10 A. M. Temperature 39.1°.

October 14. 10 A. M. Temperature 39.2°. 11 A. M. Killed with chloroform.

Autopsy.—Performed at once. Both lungs are slightly emphysematous. The inflammatory change is confined to the posterior lobe of the left lung. The diaphragmatic surface of this lobe is dark red, rather dry, and shaggy in places from tags of fibrin. The subjacent lung tissue is solid and airless forwards for a distance of 1.5 cm., except along the superior margin and at the external angle, where it is only half consolidated. The irregularly light and dark red consolidated portion gives way anteriorly in an uneven line to grey and red lung tissue, very moist and containing much air until about the middle of the lobe, from where onwards to the anterior tip the tissue is only more moist than normally, being neither consolidated nor congested. The tip is bound firmly by a fibrinous deposit to the contiguous middle lobe and is superficially solid for an area of about 1 sq. cm.

The consolidation described first comprises about one fourth of the lobe. No bacteria are seen in smears; but there is a scant growth of pneumococcus in transplantations.

In sections the alveoli near the base of the lobe are fairly regularly filled with polymorphonuclear cells in various stages of disintegration. Farther forwards, serum and large mononuclear cells appear and come to make up most of the exudate, until, at the limit of the consolidated part, there is only a small quantity of precipitated albuminous material in the alveoli. Many of the large mononuclear cells contain one or more poorly staining polymorphonuclear cells.

At the base of the lobe fibrin is abundant on the surface of the pleura and within the subjacent alveoli. Farther forwards there is little.

Fatal Cases.—In the fatal cases the clinical course of the disease and the anatomical changes are quite different from what has just been described. As already stated, a certain relation was found to exist between the quantity of culture injected and the severity of the disease produced. Most of the deaths followed the injection of a large quantity of culture, and, conversely, the injection of a large quantity was usually fatal.

The animals instead of beginning to improve on the day after the injection become worse; the fever persists; the animal does not eat, is prostrated, and dies in from two to four days after inoculation.

There is a corresponding difference in the anatomical changes. At least one lobe, and sometimes two or even three lobes are entirely consolidated. The pleural cavities contain a large quantity of bloody fibrino-purulent exudate, the pericardium is inflamed, and a septicemia exists. The exudate within the lung and in the pleural and pericardial cavities contains, as well as the blood, large numbers of capsulated pneumococci in pairs and short chains. There is an acute splenic tumor. Of the ten fatal cases, all except three presented serositis and septicemia. In two of the three instances where these complications did not occur there were several foci of necrosis in the consolidated lobes, with which a spore-bearing bacillus was associated; and death was probably due to this secondary effect.

Thus anatomically and bacteriologically the fatal type of the experimental disease resembles even more closely acute lobar pneumonia in man than the mild type.

ILLUSTRATIVE PROTOCOL.

Dog 16.—Weight, 4.5 kilos.

April 7, 1910. 10 A. M. Temperature 39°. 11.30 A. M. Under ether anesthesia, injected intrabronchially 8 c.c. of an 18 hour plain broth culture of pneumococcus N. I. Quick, complete recovery. 5 P. M. Moderately ill; temperature 39.5°.

April 8. 9.30 A. M. Worse; temperature 39.8°.

April 9. 10 A. M. Very ill; weight, 4.5 kilos; temperature 40.1°. 3 P. M. Found dead.

Autopsy.—Performed at once. The right pleural cavity contains about 20 c.c. of blood-stained, purulent exudate with many flakes and masses of fibrin. The pleural surfaces are bright red and shaggy in places from deposits of fibrin. The left pleural cavity contains no fluid, but there is congestion and a dry fibrinous exudate over the anterior lobe.

The anterior lobe of the left lung and the middle and internal lobes of the right lung are solid and airless. There are also two areas of consolidation in the right posterior lobe comprising about one fourth of its volume. The anterior lobe of the right lung is collapsed; the middle and posterior lobes of the left are emphysematous. The pericardial cavity contains 4 c.c. of bloody purulent fluid with a large clump of fibrin.

In smears from the consolidated lobes and the pleural and pericardial exu-

dates, there are enormous numbers of pointed, capsulated, Gram positive diplo-
cocci in pairs and short chains. In the heart's blood there are also large num-
bers. Transplantations from these sources give profuse pure cultures of
pneumococcus.

Sections from the anterior lobe of the left lung and the internal lobe of the
right show alike an evenly distributed purulent exudate filling the alveoli com-
pletely. There are very few red blood cells in any alveoli. Nearly all of the
alveoli contain fine granules of fibrin.

Statistical Data.—The series comprised forty-eight animals. Ten
died, thirty-four were killed within from one to twelve days, and
four, several weeks after the injection was made. Of the forty-four
that died or were killed within twelve days of inoculation, forty-
two were found to have pneumonia. In the remaining two the
lungs were normal. One of the latter animals formed part of an
experiment in which four were used to determine whether a large
quantity of culture would prove constantly fatal. The four animals
were injected one after another, each with fifteen cubic centimeters
of the same lot of culture. Three of them became very ill and died
in one and a half, one and a half, and four and a half days, respec-
tively. In two, the whole, and in the third three fifths of the right
posterior lobe was consolidated. All had empyema, pericarditis, and
septicemia. It is from their protocols that the description of the
fatal disease as given is partly drawn. The fourth animal was not
ill, had no fever, and when killed on the eleventh day, the lungs
were found to be normal. The other negative result consisted of an
animal which received six cubic centimeters of culture and was
killed on the fourth day afterwards.

It is quite certain that in the two failures the tube, instead of being
introduced through the larynx, was by mistake pushed down into
the esophagus.

The lungs of the four animals that were killed several weeks after
the injection were normal, which finding is in agreement with the
progress of resolution and the time required for its completion
according to our description.

Pneumococcus mucosus.—Besides the typical pneumococcus, we
have injected dogs in the same way with a virulent culture of *Pneu-
mococcus mucosus* (Schotmüller's *Streptococcus mucosus*) recently
grown from the spinal fluid of a case of meningitis. This organism

produced virtually the same kind of extensive fibrinous consolidation as the typical pneumococcus, the only difference being that the *exudate was more moist and quite viscid.* This difference was probably dependent upon the inherent characteristics of the organism itself rather than upon any essential difference in the character of the exudate furnished by the host. When cultivated upon artificial media, the organism manifests the same character of greater moisture and viscosity of growth as compared with the pneumococcus.

Friedländer's Pneumobacillus.—Two experiments made in the same way with a culture of the Friedländer bacillus pathogenic for mice, resulted in the production of an evenly distributed consolidation affecting nearly the whole of one lobe. The consolidated part was of a lighter red color than that produced by the pneumococcus, even grey in places, less friable, and extremely moist and viscid— peculiarities which are described as characteristic of lobar pneumonia in human beings when caused by this organism.

Control Experiments.—In several control experiments, salt solution, broth, serum, and mixtures of serum and soap solution were injected in the same way as the cultures. In none did consolidation follow.

Likewise a number of experiments made with a pathogenic streptococcus and with the influenza bacillus, which are not detailed here as they are apart from the purpose of this paper, may be considered as controls, for these bacteria produced a kind of inflammation which could not be mistaken for, or confounded with, the consolidation caused by the pneumococcus.

We may mention, finally, that in a few of the animals respiration and heart action stopped during the preliminary etherization and the animals had to be resuscitated by means of intratracheal insufflation. The intrabronchial injection of the culture followed immediately on the resuscitation. This incident had apparently no unfavorable influence upon the course of the pneumonia; all the animals survived and the course of the disease was a mild one.

DISCUSSION.

By means of an intrabronchial insufflation of a pneumococcus culture we succeeded in producing lobar pneumonia in dogs. In forty-

two successive experiments there was not a single failure. The failures in the two additional cases were due to errors in the technique, the tube being introduced into the esophagus instead of into the trachea. The anatomical and bacteriological findings in the successful experiments accorded essentially with those usually found in cases of fibrinous pneumonia of man. The consolidations were massive and lobar, and not patchy or lobular. As in croupous pneumonia, distinguished from the lobular and pseudolobar varieties, the inflammation was confined to the specialized terminal portions of the respiratory tract—the alveoli and infundibula; the mucosa of the bronchi remaining uninvolved. The interrelations of microörganisms, leucocytes, and the large mononuclear lymphocytes according to the stages of the inflammatory process, resembled those occuring in lobar pneumonia in man.[11] The findings in the fatal cases were strikingly similar to those in some fatal cases of pneumonia in man; such as pericarditis, empyema, septicemia. The mortality of the cases uncomplicated by secondary infections was at least as high as in lobar pneumonia in man: 7 in 41, or 16 per cent. At the same time, we ought to bear in mind that, among the non-fatal cases, animals are included which were killed on the first or second day, some of which, if left to themselves, might not have recovered.

However, in one respect the experimental pneumonia in our dogs differed from pneumonia in man, and that is in the clinical course of the non-fatal cases. In man, the temperature, as a rule, remains continuously high for a week or longer, and the disease terminates mostly by crisis. Furthermore, the critical termination of the clinical symptoms seems to coincide with the onset of resolution. In other words, the clinical symptoms in man seem to run parallel with the anatomical changes. This was not the case in the non-fatal cases of our experiments. While the pathological processes even in the milder cases were, in character as well as in duration, similar to those of pneumonia in man, the clinical course of the non-fatal cases was, as compared with the pathological processes, short and mild; fever and recognizable malaise subsided by lysis in a day or two.

[11] One distinguishing feature not itself essential to the process should be noted. The transition from red to grey hepatization was wanting.

This discrepancy may be explained by one or two assumptions. Doubtless the pneumococcus employed for injection was not "adapted" to dogs as the pathogenic pneumococci, producing pneumonia spontaneously, are adapted to man. Whether such an adaptation could be secured by successive passages so as to lead to a disease simulating more closely in clinical aspects the human affection, is a matter of speculation. It may be, furthermore, that dogs, unless overwhelmed with fatal doses of the virus, are less apt to respond with general reaction—perhaps just because they respond with a strong local reaction of the lungs.

However, whatever the cause, it does not affect the significance of the results, which show that by an intrabronchial insufflation of a pneumococcus culture, pulmonary inflammation may be produced, which from a pathological point of view resembles closely lobar pneumonia of man.

We believe, therefore, that these results furnish the first unmistakable experimental evidence of an intimate etiological relationship between the pneumococcus and lobar pneumonia. Attention is invited to the fact that the dogs were not prepared in any manner, or specially selected. Nevertheless, they responded to the infection with a definite pneumonic reaction. Hence the causation of the pneumonia and its outcome depended entirely upon the invading organism, its numbers and virulence; and the condition of the host was an inconsiderable factor in the result.

The essential reason for our experimental success, we believe, is contained in the fact that the injected quantity of the culture was sufficient to obliterate a group of small or even larger bronchi.

In this manner, the lumina of the bronchi and the corresponding alveoli were converted into closed cavities or semi-solid masses which contained numerous pneumococci in close proximity to the pulmonary tissue. It seems to us that the simple presence of pathogenic bacteria on a free non-denuded surface does not readily call forth a local reaction and an infection. The injections of small quantities of a culture into the trachea usually failed to call forth a pulmonary reaction, because the small quantity of the injected culture had to spread over large areas; and even if some of it reached certain bronchi or alveoli, the quantities were too minute to

cause the obliteration of even very small pulmonary areas. Pathogenic bacteria call forth an inflammatory reaction only when they have a chance to settle and develop their activities in the meshes of the various tissues or in closed narrow tubes and the small cavities of the body. The simple presence of pneumococci in the mouth does not produce an infection. Neither would these organisms be capable of producing an infection and inflammatory reaction in the pulmonary alveoli if they were free there or imbedded in masses too minute to obliterate these spaces. A quantiy of six cubic centimeters of a broth culture suffices apparently for dogs, to obliterate a fairly large number of bronchi and thus give the organisms therein a chance to cause a fairly extensive inflammatory reaction. But in these cases the local and general defensive elements of the tissues and the fluids of the body were sufficient to antagonize the infective and toxic action of the relatively large number of pathogenic organisms contained in this quantity. When, however, larger quantities of the culture were injected and larger areas of the lungs were converted into battle grounds, the local and general defences often failed to resist the too numerous invaders, and a lethal result was often produced. According to this view, the question of experimental success does not depend so much upon the alteration of the power of resistance of the invaded individual, as upon the opportunity offered to the invading pathogenic organisms for intrenchment in the invaded territory.

SUMMARY.

The numerous attempts made in the last twenty-five years to reproduce lobar pneumonia in animals practically failed in all instances.

By intrabronchial insufflation of pure cultures of pneumococcus in dogs, we produced experimental pneumonia successively in forty-two cases, with a mortality of at least 16 per cent. The fatal cases resembled closely lobar pneumonia in man. In the non-fatal cases, the pathological and bacteriological findings were again in accord with the findings in man. Clinically, however, the cases of non-fatal experimental pneumonia run a milder and shorter course than in man.

In a few instances, lobar pneumonia has been produced experimentally also with the *Pneumococcus mucosus* and with Friedländer's pneumobacillus. The anatomical findings in these experiments have shown some characteristics agreeing with the findings in the pneumonias of man produced by these organisms.

The quantity of the injected culture seemed to have a definite influence upon the outcome of the disease; in the fatal cases larger quantities of the culture had been injected.

The animals were neither selected nor prepared in any manner. The experimental success did not, therefore, appear to depend upon the degree of resistance of the individual hosts.

It is suggested that the uniformly successful results of the experiments were due to the obliteration of a large number of bronchi by the injected culture, through which mechanical effect a favorable opportunity was provided the pneumococci to develop and display their pathogenic activities consisting in the calling forth of a characteristic local, more or less effective, widespread, inflammatory reaction of the lung tissue.