THE PATHOGENESIS AND PATHOLOGY OF EXPERIMENTAL TYPE I PNEUMOCOCCIC PNEUMONIA IN THE MONKEY*

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PLATES 6 TO 10

The monkey has been employed in only a few instances for the investigation of experimental pneumococcic pneumonia. Among the reported studies, in which this animal was used, those of Blake and Cecil (1) and Schöbl and Sellards (2) give detailed observations concerning the pathology and pathogenesis of the disease. Stuppy, Falk, and Jacobson (3) were concerned principally with the production of Type I pneumococcus pneumonia in the Macacus rhesus and Cebus capucinus species. Francis and Terrell (4) studied the production and clinical course of Type III pneumococcus pneumonia in the Java monkey, Macacus cynomolgus. They used both the intratracheal and intrabronchial methods of inoculation. With the intratracheal method it was noted that the inoculum was more widely distributed in the lungs than when the intrabronchial procedure was employed. Similar lesions, as observed by X-ray, eventually developed, however, following either technique of production.

Blake and Cecil used the intratracheal method of inoculation during their studies and concluded that the resulting pneumonic infection simulated in every way that which occurred spontaneously in man. Concerning the mechanism of lobar consolidation, they, further, concluded that the pneumococci penetrated directly through the epithelium of the main bronchus of the lobe near the hilum and spread rapidly throughout the lobe by way of the perivascular and peribronchial tissues and lymphatics into the alveolar walls where they then passed into the air spaces simultaneously with the outpouring of the exudate. More recently Robertson and co-workers (5–7), Gunn and Nungester (8), Wood (9), and the author (10), using the intrabronchial method of inoculation and different animal species, also noted the similarity between the experimental pneumococcal infections and those which occur spontaneously in man, but their findings did not support those of Blake and Cecil, concerning the manner by which the organisms spread within the lungs. Rather they confirmed the views of Loeschcke (11) who concluded, from his studies of the pathogenesis and pathology of the pneumococcic pneumonia in man, that the pneumonic process was primarily intraalveolar and intrabronchial, and that the pneumococci were carried in the edema fluid directly from alveolus to alveolus through the pores of Kohn (12) and from bronchiole to bronchiole as a result of repeated aspirations, aided by breathing, coughing, and gravity.

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The intrabronchial method of inoculation, as perfected by Terrell, Robertson, and Coggeshall (13) for their study of pneumococcic pneumonia in the dog, enables one to control and determine accurately the initial site or sites of involvement, thus making it better suited than the intratracheal technique for the study of the development of lobar consolidation. An investigation of the pathogenesis and pathology of pneumococcus pneumonia in the monkey, during which the intrabronchial technique of production was used, has not been reported. It seemed advisable to carry out such a study because the earlier views of Blake and Cecil, concerning the pathogenesis of lobar consolidation in the monkey, have not been substantiated by more recent studies of this phase of pneumonia occurring in man (11, 14–16) and induced, by this method, in other animal species. To compare accurately the development of lobar consolidation in this series of monkeys with that recently observed in the dog, the same general plan of infecting and sacrificing the animals, and preparing the lung specimens for microscopic study was followed (10).

**Materials and Methods**

Fourteen apparently healthy *Macacus rhesus* monkeys were used. Their lungs were shown to be free from tuberculosis by x-ray. The intrabronchial technique of infecting the animals was, briefly, as follows. The animal was placed under morphine anesthesia, and its larynx cocainized, after which pneumococci suspended in a starch-paste medium were injected into the lungs through a radio-opaque ureteral catheter (No. 8), introduced through the trachea, into one of the lower lobe bronchi, with the aid of a fluoroscope. Type IA strain of pneumococcus was used as the infecting agent. This organism, when injected intraperitoneally, killed mice regularly in dilutions of $10^{-4}$. The dosage varied from 0.01 cc. to 0.02 cc. of an 18 hour broth culture suspended in 0.5 cc. of 5 per cent starch-broth mixture. Monkey 1-37, killed 1½ hours after inoculation, received 0.4 cc. of pneumococci suspended in 2 cc. of starch in two sites in each lower lobe.

The clinical course of the disease was followed by daily temperature, pulse, and leucocyte counts. X-rays were taken at 24 hours on those animals allowed to survive longer than this time. Blood cultures were taken on eight of the animals. The animals were sacrificed at 1½, 2½, 4½, 9, 14½, 22, 28, 36, 48, 60, 70, 72 hours, 4 and 7 days after inoculation. Each animal was killed with a lethal dose of pentobarbital sodium, after which its chest was quickly opened, the aorta clamped, and a ligature placed about the base of the heart to keep the blood in the pulmonary vessels. The pneumonic lungs were then filled with Zenker-formalin fixing solution (10 per cent formalin in Zenker's fluid without acetic acid) through the trachea and allowed to fix for from 6 to 10 hours. After this time specimens were cut from the involved lobes, washed, dehydrated, embedded in celloidin, sectioned (8 to 10 micra), and placed serially on slides, after which they were stained by Maximow's hematoxylin-eosin-azure II method (17).
Clinical Observations

The animals remained under the effect of the morphine for about 14 hours. The nine animals killed after 22 hours appeared ill. They failed to eat and were less active. Their respiratory rates were increased and some exhibited pain in the chest when handled. At 24 hours all nine animals had a leucocytosis and elevated temperatures. Two of the animals killed at 2½ and 4 days after infection were moribund and had subnormal temperatures and low leucocyte counts. All the other animals had a leucocytosis at the time of sacrifice, except the one killed the 7th day after inoculation and 3 days after recovery.

Blood cultures were taken on the animals killed at 14, 22, 36, 48, 60, 72, 96 hours, and 7 days after infection, and all were positive for Type I pneumococci. Monkey 76 killed after 2½ days of infection had over a thousand colonies at 24 hours, and at the time of sacrifice 370 colonies per cc. of blood. Monkey 81 had 16 colonies per cc. of blood at 24 hours and thousands at the time of sacrifice 4 days after inoculation. Monkey 82, sacrificed at 7 days, had 188 colonies per cc. of blood at 24 hours, and at 5 days its blood was sterile. The remaining animals on which cultures were taken had thousands of colonies per cc. of blood at the time of sacrifice.

Pathogenesis of the Lesions

Macroscopic Observations.—As the lungs of all the animals were fixed intratracheally, immediately after death, only a hurried inspection of the pleural surfaces of the pneumonic lesions was made. The maximum consolidation occurred within 22 hours after inoculation. Monkey 1-32, killed at 48 hours, had approximately 3/4 of the inoculated lobe consolidated. All the other animals killed after 22 hours had 3/4 or more of the inoculated lobes consolidated. Spread of the infection to other lobes occurred only in monkey 1-39, killed at 14 hours. In this animal, portions of the left upper and left lower lobes as well as the inoculated right lower lobe were consolidated.

The inoculated lobes of the six animals killed at increasing intervals within 22 hours after infection showed a regular increase in the extent of consolidation, which progressed from the periphery of the lungs at the site of inoculation toward the hilum. The pneumonic areas, enlarging in a contiguous manner, were deep red, slightly retracted, irregular in outline, and edematous at their spreading margins. In all the animals there was a sharp line of demarcation between the consolidated and unconsolidated portions of the lobes. The consolidated lobes were always smaller than the corresponding opposite uninvolved lobes. Fibrin was present on the pleural surfaces in some of the animals. The consolidated lobes of the animals killed within 28 and 72 hours after inoculation had essentially the same grayish-red appearance. Monkey 82, killed at 7 days after infection, had recovered and the inoculated lobe was air-containing and showed only slight discoloration.

Microscopic Observations.—The inflammatory reaction had already begun 1½ hours after inoculation (Fig. 1). It had a bronchial or focal distribution. The initial exudate consisted of edema fluid in which were a few red blood cells and blood leucocytes and pneumococci. There was no detachment of the septal cells, but the capillaries were greatly congested with leucocytes (Fig. 1). At 2½ hours the focal areas
of inflammation were larger and showed large numbers of leucocytes leaving the septal capillaries and entering the air spaces (Figs. 2 and 3). At 4½ hours the alveoli and bronchi were more or less filled with the serous and cellular exudate, although the extent of consolidation was small (Fig. 4). The margins of the consolidated areas showed only an edematous exudate and a beginning migration of leucocytes from the blood as was present in the 1½ hour lesion. The borders of the increasingly larger areas of consolidation in the lungs of the animals killed at 9, 14½, and 22 hours had this same appearance (Figs. 9 and 10) with the older portions showing increasing numbers of cells in the exudate (Figs. 8, 11, and 12). Twenty-two hours after infection the alveoli and bronchi were more or less uniformly filled with exudate (Fig. 12).

The serum and blood leucocytes entered the air spaces principally through the small blood vessels, and capillaries in the alveolar walls (Fig. 3). There was some perivascular and peribronchial edema and varying degrees of interstitial cellular infiltration in different parts of the lung lesions of the six animals killed during the first 24 hours of the disease when maximum consolidation took place. The interstitial reaction, however, bore no relation to the extent or intensity of consolidation. Areas showing no interstitial reaction (Fig. 12) were as intensely consolidated as other regions which also showed peribronchial and perivascular edema and cellular infiltration. Interstitial and lymphatic involvement were more pronounced in the 1½ to 4 day lesions, yet the reaction within the air spaces during this time was one of gradual recovery (Figs. 15 to 19).

Distribution of Pneumococci.—In the consolidated lobes of the five animals killed within the first 15 hours after inoculation, pneumococci were seen only in the alveolar and bronchial exudates and in large numbers after 4 hours (Figs. 6 and 7). The greatest number of organisms were in the alveolar and bronchial spaces at the spreading border of the lesions where the exudate consisted principally of edema fluid (Figs. 6, 9, and 10). In the older consolidated portions of the lesions organisms were seen in varying numbers both free and in leucocytes. No organisms were seen in the substance of the alveolar walls in any of the developing lesions, but beyond their margins many were lying in a thin layer of edema fluid on the alveolar surfaces and in the pores of Kohn of apparently normal alveoli (Fig. 6). Likewise, none were seen at points in the septa where the leucocytes were entering the spaces (Fig. 3). Pneumococci were not seen invading the bronchial epithelial cells, although in the early lesions large numbers were seen in the exudate lying on their free surfaces.

An occasional pneumococcus was seen in the edematous interstitial tissue of some bronchial and blood vessel walls in the lesions of the animals killed at 28, 36, 48, 60, 72, and 96 hours after infection. Pneumococci were not seen in the small or large perivascular, peribronchial, or pleural lymphatics in the lesions of any of these animals and were demonstrable only in the blood vessels and septal capillaries of two animals which were moribund and had marked bacteremias at the time of sacrifice, 48 and 96 hours after inoculation. Only an occasional pneumococcus was seen in the blood of the animal killed at 48 hours, while large numbers were present both free and in polymorphonuclear and monocytic leucocytes within the vessels and capillaries of the one killed at 4 days after infection (Fig. 19). Small thrombi containing large numbers of organisms were present in the lung capillaries and larger pulmonary vessels of this animal.
In spite of the increased and persistent interstitial inflammation of the pneumonic lungs (Figs. 17 and 18) and bacteremias in the animals killed after the first 24 hours of the disease, pneumococci diminished in numbers from the bronchial and alveolar exudate. They were found only in small numbers in the exudates of the animals killed at 28, 36, 48, and 60 hours, and were not seen in the exudates of those killed at 3, 4, and 7 days after infection. At the same time the organisms disappeared from the exudate, the cellular elements changed gradually from polymorphonuclear leucocytes to large, markedly phagocytic mononuclear cells.

**Histogenesis of Cells in the Exudate**

With the exception of a few old, free, carbon-filled macrophages, which are normally present in the alveoli, the blood leucocytes were the first cells to appear in large numbers in the exudate. Within 1½ hours after inoculation polymorphonuclear leucocytes had collected in large numbers in the capillaries and small blood vessels in the alveolar walls, and a few were already in the air spaces (Fig. 1). The migration of leucocytes from the capillaries and blood vessels followed rapidly the outpouring of edema fluid into the alveolar spaces, and continued until the greater portion of the inoculated lobes were consolidated. The leucocytes entered the alveoli principally through the septal capillaries and small blood vessels (Fig. 3). Leucocytes in all stages of passing from the alveolar capillaries could be seen throughout the lesions and especially in areas near the margin of the spreading borders in the animals killed during the first 24 hours. As they entered the air spaces, the leucocytes, both granular and non-granular varieties, formed asteroid configurations along the septa (Fig. 3). In some areas a few passed directly through the larger pulmonary vessels and vessels in the bronchial walls into the edematous interstitial tissue, but leucocytes were present only in relatively small numbers in the interstitial tissue in the lesions of the animals killed within 24 hours after inoculation (Figs. 1 to 12). The polymorphonuclear leucocyte was the predominant cell type in the exudate during the first 36 hours after infection. During this time they phagocytized varying numbers of pneumococci and began to degenerate so that by 72 hours the majority were degenerating and being ingested by the mononuclear macrophages. None were present in the alveolar spaces of the clearing 7 day lesion.

The non-granular leucocytes (lymphocytes and monocytes) entered the exudate along with the polymorphonuclear leucocytes throughout the early stages of the disease. At first they were inconspicuous in the exudate because of the predominance of polymorphonuclear leucocytes. Only a few were in the exudate in the 2½ hour lesion (Fig. 3), but they became increasingly more numerous in the 4½, 9, and 14½ hour lesions (Figs. 7, 8, and 11). After entering the exudate the hematogenous mononuclear exudate cells did not degenerate, but soon began to hypertrophy and transform themselves into actively phagocytic cells. The morphological transformation of the lymphocytes into monocytes and monocytes into macrophages was clearly seen by examining the exudates in consecutively older lesions within the first 36 hours of the disease. In the 9 hour lesion (Fig. 8) the mononuclear exudate cells were larger and more numerous than in the 4½ hour lesion (Fig. 7), but the majority of these cells at this time resembled the lymphocytes still within the blood vessels.
In the 14½ hour lesion (Fig. 11), they were definitely larger than those seen in the 9 hour lesion (Fig. 8). Their nuclei were less compact and assumed many shapes. They had accumulated more cytoplasm which was less basophilic than that of the cells in the 9 hour lesion. Many of these cells resembled monocytes of the blood, but the great majority of the cells still within the vessels were of the lymphocytic variety. The larger of the “polyblastic” mononuclear cells in the 14½ hour lesions had begun to phagocytize red blood cells and an occasional pneumococcus. In the 22 hour lesion, near the site of inoculation (Fig. 13), the mononuclear exudate cells were still larger and more phagocytic than those seen at 14½ hours. In the exudate at the margin of the 22 hour lesion (Fig. 14) which was more recently involved, they were smaller and resembled those in the 9 and 14½ hour lesions.

By 28 hours the majority of the lymphocytes and monocytes had assumed the morphology and function of macrophages which were still larger and actively phagocytizing large numbers of degenerating granular leukocytes, red blood cells, and pneumococci in the 36 hour lesion (Fig. 15). After this time only an occasional small hematogenous mononuclear cell was seen in the exudate, which consisted principally of typical large mononuclear cells with ingested constituents, in various degrees of digestion in their cytoplasm (Fig. 16). During the first 36 hours of the disease when the transformation of the non-granular leukocytes into larger phagocytic cells took place, the local tissue cells showed only swelling and no proliferation. There was no evidence in any of the lesions that the hematogenous mononuclear exudate cells degenerated after they entered the exudate.

The septal cells (alveolar epithelium) did not become detached or show any significant change as a result of the marked exudation of serum and leukocytes from the blood during the first 24 hours of the disease (Figs. 3 to 13). The enlargement of the septal cells was gradual and associated with swelling of other cellular constituents (capillary endothelium and fibroblasts) in the alveolar walls. By 36 hours septal cells were conspicuous on the walls where they had accumulated large amounts of foamy cytoplasm, but no mitotic figures indicating proliferation were seen in them (Fig. 13). Mitotic figures were rarely seen in these cells, and then only in the 2½, 3, and 4 day lesions. At this time binucleated cells appeared on the alveolar walls. These binucleated cells were still numerous on the septa in the 4 and 7 day lesions which were undergoing resolution and showing diminishing numbers of macrophages in the exudate (Figs. 18 to 20). No phagocytosis of pneumococci, red blood cells, and polymorphonuclear leukocytes by the attached single or binucleated septal cells was noted in any stage of the disease. Single or binucleated mononuclear cells, which did not contain ingested material in their cytoplasm and which resembled the attached cells, were seldom seen free in the spaces. The septal cells remained enlarged and numerous on the walls in the 4 and 7 day lesions which were undergoing resolution (Figs. 19 and 20).

The bronchial epithelium showed no injury, proliferation, or phagocytic activity in any of the lesions, although it became infiltrated with polymorphonuclear leukocytes in the early stages of the disease. The endothelial cells lining the pulmonary vessels, capillaries, and lymphatics, showed no proliferative activity at any stage, or phagocytosis of organisms in the 2 and 4 day lesions in which intravascular pneumococci could be seen. There was no evidence of proliferation of the fixed tissue histiocytes.
in the interstitial tissue of the bronchi, pleura, and blood vessels with their subsequent migration into the alveolar spaces to contribute to the source of the mononuclear macrophages in the exudate. Likewise, as far as could be determined, the old pigment-filled macrophages in the interstitial tissue did not migrate into the exudate in response to the acute infection. On the other hand, the resolving lesions showed an increased number of macrophages in the interstitial tissue. These were morphologically identical with the diminishing macrophages still in the alveolar spaces. A few smaller basophilic mononuclear cells accumulated in the interstitial tissue in the older lesions. These resembled lymphocytes, monocytes, and plasma cells.

DISCUSSION

The clinical manifestations of pneumonia in this series of animals were similar to those observed by Blake and Cecil (18), Schöbl and Sellards (2), and Francis and Terrell (4) in larger series of monkeys, and by Terrell, Robertson, and Coggeshall (13) in experimental pneumonia in the dog. Although most of the animals were killed within 4 days after inoculation, the early severe bacteremias in all but one, on which cultures were taken, indicated that, if allowed to survive longer, the majority would have eventually succumbed to the infection. At the time of sacrifice the animals varied greatly in severity of illness. The histological findings, however, could be more closely correlated with the age of lesions, than with their gross appearance or the clinical condition of the animals at the time of death.

The evolution of the inflammatory process in the lungs was rapid, progressive, and similar to that seen by Robertson, Coggeshall, and Terrell (5), and the author (10) during their studies of pneumonia in the dog. Lobar consolidation took place within 24 hours after inoculation. The consolidated lobes of animals killed within the first 72 hours had essentially the same gross appearance; but during this time, the exudate changed gradually from one composed of edema fluid, polymorphonuclear leucocytes, lymphocytes, monocytes, red blood cells, and many pneumococci to one of large mononuclear macrophages. By the 4th day resolution was well advanced, and practically complete by the 7th day. The cellular changes in and the disappearance of pneumococci from the exudate took place in spite of early persistent bacteremias and increasing amounts of interstitial and lymphatic involvement. Similar changes were reported by Robertson and Loosli (19) in the pneumonic exudate in dogs showing severe infections and dying on or after the 4th day of illness. Francis and Terrell also noted by x-ray in monkeys that lobes which became consolidated by 24 hours after inoculation showed varying degrees of clearing on the 3rd or 4th day of the disease, although during this time some of the animals had developed bacteremias and had a spread of their infections to other lobes.

The histological changes, the kinds of cells, and the sequence with which they appeared in the exudate were similar to those seen in the induced pneu-
monic lesions in dogs (10). The polymorphonuclear leucocytes appeared early and in larger numbers, but they began to degenerate and be taken up by the mononuclear macrophages after 24 hours. The mononuclear exudate cells presented a great variety of sizes, shapes, and degrees of phagocytic activity depending on the age of the consolidations. By observing them in consecutively older lesions, it could be seen that the "polyblastic" mononuclear cells represented transitional stages in the development of the small hematogenous mononuclear exudate cells (lymphocytes) which appeared early in the exudate, into larger mononuclear phagocytes. The transformation of the lymphocytes into monocytes and monocytes into typical macrophages was more or less completed during the first 36 hours of the disease. By examining only lesions of animals killed after this time, one could readily get the impression that the large mononuclear phagocytic cells arose only locally from the swollen septal cells, as is generally considered to occur both in the case of pneumonia in man and experimental pneumonia in animals (10).

It was impossible, however, to determine to what extent the septal cells contributed to the source of the free macrophages, for large numbers of the latter cells, which were derived from the hematogenous mononuclear cells, were present in the exudate before the local tissue and septal cells began to show a reaction to the invading organisms. By studying the septal cells in consecutively older lesions from the beginning of consolidation until resolution was complete, it appeared that their reaction was one principally of swelling with occasional division to form binucleated attached cells. Similar observations were noted during the study of the septal cell reactions in pneumonic lesions in dogs. A more extended consideration of the histogenesis of cells in pneumococcic pneumonia has been given in this report (10).

The observations concerning the development of lobar consolidation in this series of monkeys were, likewise, similar to those noted during the study of the histogenesis of cells in experimental pneumonia in the dog (10). In the early lesions the pneumococci were distributed principally within the air spaces, and were most numerous in the edematous exudate, which was abundant, at the spreading borders of the consolidated areas. The progressive and contiguous enlargement of the areas of inflammation occurred as a result of the spread of the infected edema fluid, which preceded the entrance of leucocytes into the air spaces, from alveolus to alveolus directly through the pores of Kohn (12) and from bronchiole to bronchiole by repeated aspirations. These findings are in agreement with those of Loeschcke (11), Heinrichs (14), Robertson and Uhley (15), and Loosli (16) concerning the pathogenesis of lobar consolidation in man, and also with the recent observations made by Robertson (6), Robertson and Hamburger (7), during similar studies in the dog, and by Gunn and Nungester (8), and Wood (9) in the rat. These studies as well as the present one show that pneumococcic pneumonia is primarily
an intraalveolar infection. They further show that the injury to the alveolar tissue and capillaries, which is followed by exudation of the blood constituents into the air spaces, can best be attributed to the soluble toxic products liberated by the pneumococci growing in the exudate rather than by direct invasion of the septal tissue by the organisms themselves, as Blake and Cecil, Schöbl and Sellards, Stillman and Branch (20), and Rake (21) concluded.

The outpouring of edema fluid appears to be typical of the body's reaction to the pneumococcus regardless of the site of inoculation as has been shown by Welch (22) and Goodner (23) in their studies of dermal pneumonia in the rabbit. That substances liberated by the pneumococcus can produce an edematous reaction when injected into the skin of man and the lungs of animals has been shown recently by Dick and Boor (24), and Sutliff and Friedemann (25). Whatever the nature of this edema-producing substance or substances might be, their injurious action is mild, for consolidation is seldom followed by necrosis of the lung tissue. The abundant fluid exudate in pneumococcic inflammations most likely does not represent a manifestation of allergy, as Loeschcke, Lauche (26), Fried (27), Heinrichs, and Lindau (28) maintain. Similar inflammatory reactions can be elicited by the pneumococcus in non-sensitized and sensitized, and in immune and non-immune animals. There is no evidence that it represents an allergic reaction in the case of pneumococcic pneumonia in man. Likewise, there was no evidence in this study to support the concept of a neurogenic factor in the production of the edematous exudate in pneumonic lesions as proposed by Reinhardt (29).

Atelectasis may serve to hold the organisms in the lungs until the inflammatory process is initiated, but it probably does not play an important part in the spread of the infection within the air spaces as Corylls and Birnbaum concluded (30). Rather, it would seem that atelectasis should prevent or hinder the spread of organisms within the air spaces.

The rapidity with which lobar consolidation occurred in this series of animals, and the distribution of the pneumococci in the consecutively older lesions would indicate that the data upon which Blake and Cecil based their concept of pathogenesis of lobar consolidation in the monkey were incomplete. They made no systematic study by x-ray of the evolution of the lesions as did Francis and Terrell, nor did they sacrifice animals at increasing intervals of time after inoculation, so that the age of the lesions could be accurately determined. Although Blake and Cecil examined the lungs of two animals sacrificed at 3½ and 12 hours after inoculation, their observations concerning the manner of intrapulmonary spread of the organisms, for the most part, were made from lungs of animals dying with pneumococcic septicemias from 3 to 5 days after inoculation.

Schöbl and Sellards, and Permar (31) also considered the interstitial tissue and lymphatics to be the chief pathways for the spread of the organisms within
the lungs in the early stages of the disease when consolidation took place. Schöbl and Selliards, however, examined the lungs of animals dying only after the 1st day of the disease. They observed no organisms but only a cellular infiltration in the interstitial tissue and congested lymphatics. Permar, using rabbits, observed organisms in the interstitial tissue and lymphatics of the lungs of animals killed only 10 hours or longer after infection. In the present study as well as that made in dogs (10), organisms were never seen in the developing lesions in the substance of the alveolar walls, in the interstitial tissue of the bronchial tree, or penetrating the bronchial epithelium as Blake and Cecil describe. Large numbers, however, were present in the bronchial and alveolar exudate of lesions comparable to their early ones. The manner of fixing the lungs for microscopic examination in this series of animals, however, aided materially in determining whether the organisms were in the tissues or air spaces. The results of this study of the distribution of the pneumococci in such prepared lungs suggest that the great majority of organisms which Blake and Cecil considered to be in the walls of the terminal bronchioles, alveolar ducts, and alveoli in their early lesion were in reality lying on the surfaces of these partially collapsed structures. In early pneumonic lesions in man pneumococci also have been infrequently noted in the interstitial tissue while large numbers have been observed in the fluid exudate in the air spaces (11, 15, 16, 33, 34). That pneumococcal inflammation of the lungs should be considered an infection of the alveolar and bronchial surfaces, as Wadsworth (35) long ago pointed out, is substantiated in this study.

Varying degrees of interstitial and lymphatic involvement were noted in this study, but it could not be correlated with the extent or degree of consolidation. Interstitial involvement was more pronounced in the lungs of the animals killed after consolidation had taken place; yet in these lesions organisms gradually disappeared from the exudate, as it changed from one of polymorphonuclear leucocytes to one of mononuclear macrophages. The exudate in the animal killed at 4 days was undergoing resolution in spite of a marked interstitial reaction and a bacteremia so pronounced that organisms could be seen in large numbers in the septal capillaries and larger pulmonary vessels. Thus the presence of organisms and exudate cells in the interstitial tissue, and organisms in the alveolar walls of animals dying of severe septicemias after 3 or 4 days of illness does not necessarily indicate an inflammatory process which will lead to consolidation of the lungs, as Blake and Cecil concluded. Certainly organisms do enter the interstitial tissue and lymphatics in varying numbers, but they do so in all probability secondarily from the alveolar spaces. Once in these channels they most likely do not reenter the alveoli, but become important as the source of infection producing complications, such as pericarditis, empyema, and bacteremia, rather than having a
part in the pathogenesis of lobar consolidation. Recent studies concerning
the lung-blood barrier in experimental pneumonia in the dog further substan-
tiate this view (36).

Blake and Cecil's observation, that the pneumococci entered the interstitial
tissue first through the bronchial epithelial lining, was not confirmed by
Schöbl and Sellards, Permar, and Gaskel (32), who used the same or similar
techniques of inoculation. They concluded that the fluid inoculum was
aspirated directly into the finer air spaces. They further pointed out that,
following the intratracheal injection of organisms, consolidation began at or
near the hila of the lobes because the fluid inoculum, with the animals on their
backs, entered directly into the most dependent short bronchial-alveolar
units in the hilar regions and that the position of the animal determined which
lobes the inoculum entered. Recently Robertson and Hamburger (7) have
shown in the dog that the pneumonic exudate must be fluid enough to flow or
be aspirated into the terminal air passages before secondary pulmonary lesions
develop. Viscid exudate, containing large numbers of organisms, placed in
the entrance of primary bronchi with the animals in a position favorable for
flow of the material into the lobe did not result in pulmonary consolidation.
There was, however, ample opportunity for organisms in the exudate to
penetrate the bronchial epithelium and produce interstitial inflammation and
consolidation. That this did not occur is further evidence against the validity
of the concept of pathogenesis of lobar pneumonia as proposed by Blake and
Cecil.

SUMMARY

The pathogenesis of lobar consolidation and microscopic pathology of
induced Type I pneumococcic pneumonia in a series of fourteen monkeys,
killed at close intervals of time after infection, have been studied. The inflam-
matory process which resulted in consolidation was primarily intraalveolar
and intrabronchial. The pneumococci spread within the air spaces as a result
of the dissemination of the infected edema fluid directly from alveolus to
alveolus through the pores of Kohn and from bronchiole to bronchiole as a
result of repeated aspiration during breathing. The pneumonic process within
the air spaces developed and progressed independently of the reaction in the
interstitial tissues. The organisms spread to the interstitial tissue secondarily
from the alveolar spaces. Once in the interstitial tissues they appeared to
be the important source of infection producing bacteremia but not important
in the mechanism by which consolidation was produced.

The exudate cells came chiefly from the blood. The large mononuclear
cells which replaced the polymorphonuclear leucocytes were derived principally
from the hypertrophy and transformation of lymphocytes and monocytes into
macrophages after they entered the exudate in the early stages of the disease. The part the local septal cells played as the source of the macrophages could not be accurately determined. The reaction of the septal cells appeared to be chiefly one of swelling without detachment and occasional proliferation to form binucleated attached cells. To follow the transformation of the hematogenous mononuclear cells into macrophages in the exudate, the inflammatory reaction must be examined at frequent intervals during the first 36 hours of the disease.

The similarity of the pathogenesis of lobar consolidation in human pneumonia to that observed in the experimentally induced disease in monkeys and dogs was discussed.

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EXPLANATION OF PLATES

Photomicrographs were made from sections stained with Maximow's hematoxylin-eosin-azure II technique.

PLATE 6

Fig. 1. Monkey 1-37M, killed 1½ hours after left lower lobe inoculation. Area at site of inoculation shows a beginning inflammatory reaction. Some septal capillaries are markedly congested with leucocytes, and some leucocytes are already in the alveoli. The granular precipitate is starch granules and serous exudate. There is no involvement of interstitial tissue of blood vessel (v) or of the lymphatics (l). × 112.

Fig. 2. Monkey 1-31M, killed 2½ hours after right lower lobe inoculation. Area near site of inoculation shows an intense inflammatory reaction. The exudate consists of edema fluid, red blood cells, and leucocytes. The vessel wall (v) shows no reaction although leucocytes have collected at the periphery of its lumen. × 112.

Fig. 3. Monkey 1-31M. Area shows large numbers of leucocytes in the process of entering the exudate at points along the septa. × 340.

Fig. 4. Monkey 1-32M, killed 4½ hours after right lower lobe inoculation. Area near site of inoculation shows continued exudation of leucocytes into the air spaces at points along the septa. The bronchial (b) and blood vessel (v) walls show only slight involvement. The lymphatic (l) is congested. × 112.
(Loosli: Type I pneumococcic pneumonia)
Fig. 5. Monkey 1-32M. Area beyond the marginal zone of edema-filled alveoli. Septal walls appear normal. Small amount of serous precipitate in some alveoli. × 112.

Fig. 6. Monkey 1-32M. Area x of Fig. 5 shows many pneumococci lying in the thin layer of edema fluid on the surface of an alveolus. No organisms are seen in the substance of the walls. × 755.

Fig. 7. Monkey 1-32M. Area near the site of inoculation. Large numbers of pneumococci are present in the exudate. None are seen in the substance of the septa. A group of leucocytes (a) are entering the exudate. A few small mononuclear leucocytes are already in the exudate. One old pigment-filled macrophage (m) is present in the exudate. × 525.

Fig. 8. Monkey 94M, killed 9 hours after right lower lobe inoculation. Area near site of inoculation shows the character of exudate. Pneumococci are seen but are fewer in number than at 4½ hours (Fig. 7). Cellular exudate consists principally of polymorphonuclear leucocytes, some containing ingested pneumococci. Numerous small hematogenous mononuclear cells are also present. Some have taken up an occasional pneumococcus. The alveolar walls appear normal. The septal cells (s) show no reaction. × 600.
PLATE 8

Fig. 9. Monkey 1-39M, killed 14½ hours after right lower lobe inoculation. Area at the spreading border of the lesion shows focal areas of cellular exudation and intervening alveoli filled with edema fluid. The inflammatory process resembles the early beginning reaction (Fig. 1) at the site of inoculation. × 112.

Fig. 10. Monkey 1-39M. Area a in Fig. 9 shows large numbers of pneumococci in the exudate with some lying across a septum in an alveolar pore (p). A few hematogenic mononuclear leucocytes are present in the exudate. The alveolar walls show no organisms in their substance. × 600.

Fig. 11. Monkey 1-39M. Area near site of inoculation shows numerous mononuclear exudate cells of many sizes and shapes. The majority are larger than those seen in the 9 hour lesion (Fig. 8). The alveoli show no pneumococci in their walls. Only a few pneumococci are seen in the exudate and these are within cells. × 600.

Fig. 12. Monkey 1-44M, killed 22 hours after left lower lobe inoculation. Area near site of inoculation shows the alveoli uniformly filled with cellular exudate. Leucocytes are still entering exudate at points along the septa. Vessel (v) walls show no involvement. × 112.
(Loosli: Type I pneumococcal pneumonia)
Fig. 13. Monkey 1-44M. Area near site of inoculation shows the character of the exudate. A few polymorphonuclear leucocytes have begun to degenerate. The majority of the mononuclear cells are larger than those seen at 14 hours (Fig. 11) and are actively phagocytic. A few smaller non-phagocytic hematogenous mononuclear cells of varying sizes, representing transitional stages in their development into macrophages, are seen. The septal cells (s) are beginning to enlarge. × 600.

Fig. 14. Monkey 1-44M. Area of more recent consolidation near the margin of the lesion shows numerous small mononuclear exudate cells similar to those within the blood vessels and in the exudate of earlier lesions (Figs. 8 and 11). × 600.

Fig. 15. Monkey 1-06M, killed 36 hours after right lower lobe inoculation. Area near the site of inoculation shows mononuclear exudate cells all of the large variety, which show marked phagocytic activity. Free pneumococci are not seen in the exudate or in the substance of the alveolar walls. The septal cells (s) are larger than those seen in the 22 hour lesion (Fig. 13). × 600.

Fig. 16. Monkey 76M, killed 2½ days after left lower lobe inoculation. The exudate cells consist principally of mononuclear macrophages which contain fragments of ingested polymorphonuclear leucocytes, red blood cells, etc. The alveolar walls are greatly swollen, and the septal cells (s) are conspicuous. No pneumococci are seen in the substance of the alveolar walls. × 600.
(Loosli: Type I pneumococcal pneumonia)
PLATE 10

Fig. 17. Monkey 76M, killed 2½ days after inoculation. Low power magnification shows a segment of a wall of a large blood vessel (v), a lymphatic vessel (l) and surrounding alveoli. The exudate cells in air spaces consist principally of mononuclear macrophages (Fig. 16), while the wall of the vessel and lymphatic shows a polymorphonuclear leucocyte reaction. Organisms are seen in the edematous interstitial tissue while the older exudate in the air spaces shows none. × 112.

Fig. 18. Monkey 81M, killed 4 days after right lower lobe inoculation. The vessel (v) wall is edematous. The lymphatics (l) are congested and some are filled with polymorphonuclear leucocytes. The exudate in the air spaces is undergoing resolution, and consists of macrophages (Fig. 19). × 112.

Fig. 19. Monkey 81M had a marked bacteremia and numerous pneumococci (p) can be seen within the septal capillaries. No organisms are seen within the air spaces or in the substance of the alveolar walls. The septal cells (s) are large and some are binucleated, but the macrophages are decreasing in numbers in the exudate (Fig. 18). × 600.

Fig. 20. Monkey 81M, killed 7 days after right lower lobe inoculation, and 3 days after recovery. Resolution is practically complete. The alveolar walls are still somewhat swollen and septal cells (s) are conspicuous but are smaller than those in the 4 day lesion (Fig. 19). Numerous binucleated septal cells (s') are present. A megakaryocyte (m) is seen in a capillary. × 600.
(Loosli: Type I pneumococcic pneumonia)