# ON THE RELATION OF BACTERIA TO SO-CALLED "CHEMICAL PNEUMONIA"

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PLATES 4 AND 5

(Received for publication, April 22, 1929)

## I. HISTORICAL

The pneumonia resulting from inhalation of irritating substances has been said to be caused purely by the chemical agents inhaled, and not to be due to the action of bacteria.

Delafield, Prudden and Wood (1) state that "the inhalation of irritating gases, especially chlorine, ammonia, nitrogen tetroxide, bromine, and a large number of the corrosive organic products now used as destructive agents in war, gives rise to a characteristic type of pneumonia due solely to the chemical action and not necessarily accompanied by bacterial infection, although this may occur."

Wood (2) reports a case of pneumonia occurring from breathing nitric oxide fumes which resulted fatally. The pneumonia was lobular in type, with desquamation of mucous membrane of trachea and bronchi, cellular plugs in the bronchi, and areas of consolidation around the smaller bronchi. The alveoli in the consolidated areas were "filled either with a transparent albuminous mass, or with fibrin containing a few leucocytes, or with desquamated alveolar epithelium, . . . . Throughout, many alveoli contained red blood corpuscles." Various staining methods showed no organisms. Wood reviewed the literature and found two cases reported by Loeschcke (3), in which a search for bacteria in sections had failed to reveal their presence. Pneumonia induced in animals with nitrogen tetroxide ($N_2O_4$) fumes was characterized by edema, fibrinous exudate, red and white cells and desquamated alveolar epithelium. Cultures were sterile.

Karsner (4) and Karsner and Ash (5) have shown that rabbits exposed to atmospheres rich in oxygen for 24 to 48 hours, develop a fibrinous broncho-pneumonia in which edema and desquamation of the alveolar epithelium play a prominent part. They think that "the absence of any well marked leucocytic infiltration in the pneumonia area and the absence of demonstrable leucocytosis in the circulating blood point toward a pneumonia of irritative rather than of bacterial origin." However, bacteriological studies of the lungs are not reported.

Wollstein and Meltzer (6) in the course of some intra-bronchial insufflations found that certain salt solutions caused pneumonia. 2 per cent sodium chloride solution, sodium sulfate, magnesium sulfate, and magnesium chloride solutions produced small patches of broncho-pneumonia. Cultures showed no growth. Mercuric chloride, 1–10,000 dilution, caused hemorrhage, edema and thrombi; no bacteria grew. In another series of experiments (7) they caused broncho-pneumonia by the injection of chloramine-T and Dakin's solution. The pneumonias produced by these solutions were characterized by the absence of fever or appearance of illness. There is no record of bacteriological studies. Kline and Meltzer (8) found that aleuronat and starch caused consolidation resembling that caused by a virulent pneumococcus. Egg yolk and lecithin caused a lobar pneumonia like that caused by a virulent pneumococcus. Cultures were sterile in the majority of their experiments. Wollstein and Meltzer (7) state that "the consolidations of the lung produced by chemical substances differ from infectious pulmonary inflammations only in their sterility."

On the other hand, Winternitz, Lambert, Jackson and Smith (9) find that after chlorine poisoning organisms "that normally inhabit the mouth of the dog find their way into the bronchi and lungs of the dog shortly after gassing and remain there for a long time in animals that survive the acute period." They show "that the pneumococcus and a small Gram-negative hemoglobinophilic organism, normal inhabitants of the dog's mouth, can be cultivated from the lung as early as one-half hour and as late as four days after gassing." Similarly, Winternitz, Lambert and Jackson (10), in studying the bacteriology of pneumonias following gassing with phosgene, found that the bacteriological findings were much the same as in cases of pneumonia in non-gassed dogs.

## II. EXPERIMENTAL

In view of the high incidence of pneumonia in the lungs of animals experimentally gassed with toxic compounds in the toxicity work, Medical Research Division, Edgewood Arsenal (11), ample opportunity was offered for the study of the types of pneumonias so caused, and of the incidence of bacteria in these pneumonias.

As cultures of the lungs had not been made at the time of autopsy, the lung sections were stained with Goodpasture-MacCallum stain in order to study the bacteria present. This had the advantage over cultures of giving the number of bacteria present, and showing their position in regard to the lung framework.

The animals studied had been placed in the ice-box as soon as they were found dead, and the autopsy performed as soon as possible thereafter. In studying the sections from these animals the time elapsing between death and autopsy was considered, but this was not found to affect the number of bacteria present when the autopsy was performed within a reasonable limit.

## III. METHODS

The tissues were fixed in Zenker-formol solution and embedded in paraffin. The lungs were fixed by running the fixing fluid into the trachea, and then immersing them in the fluid for 24 hours before any sections were taken, as this has been found necessary to preserve the delicate structure and prevent artifacts (12). The sections were stained with hemotoxylin and eosin to study the types of pneumonia, and with Goodpasture-MacCallum stain to study the bacteria present.

## IV. DISCUSSION

The types of pneumonia and the bacteria present were studied in the lungs of dogs gassed with mustard gas, methyldichlorarsine, lewisite, phosgene, and some miscellaneous gases.

The significance of the number of bacteria present was considered in reference to:

A. The kind of gas inhaled.
B. The type of pneumonic exudate.
C. The temperature of the animal during illness.
D. The length of time between death and autopsy.
E. The survival after gassing.
F. Bacteria in non-gassed lungs.
   1. In normal lungs.
   2. From pneumonia experimentally caused.
   3. From cases of pneumonia occurring spontaneouslv in dogs.

### *A. Relation of Bacteria to the Kind of Gas Inhaled*

*1. Mustard.*—The lungs of mustard gas poisoning show the following lesions in the order of their frequency: hemorrhage; atelectasis; edema; and exudate consisting of epithelial cells, leucocytes, and mononuclear cells, but very little fibrin. In a majority of cases epithelial cells and polymorphonuclear leucocytes are present in large numbers. In a few cases epithelial cells and mononuclears prevail.

Of thirty-two cases studied, nine showed a few bacteria, sixteen showed many and seven a large number. There was no correlation observed between the type of exudate and the number of bacteria.

Table I gives a few typical cases.

*2. Methyldichlorarsine.*—The pneumonia in methyldichlorarsine poisoning consists of an exudate in which epithelial cells and mononu-

clears predominate. In only a few cases are they out-numbered by polymorphonuclear leucocytes.

In the lungs of eighteen cases, twelve showed few bacteria, two showed many, and four large numbers.

TABLE I

*Results Showing Number of Bacteria in a Few Typical Mustard Lungs*

| General condition of lung | Pneumonic exudate | Bacteria |
|---|---|---|
| Hemorrhage<br>Atelectasis | None | Few |
| Solid with exudate | Leucocytes | Very few |
| Nearly normal on recovery from gassing | Organized areas and desquamating epithelial cells | Large numbers |
| Hemorrhage<br>Atelectasis | Leucocytes, epithelial cells | Few |
| Congestion<br>Hemorrhage | Epithelium, leucocytes | Many |
| Congestion<br>Hemorrhage<br>Edema | Bronchial exudate | Many |
| Fibrin, edema | Leucocytes, epithelial cells | Many chains |
| Necrotic areas | Leucocytes, mononuclears | Enormous numbers in necrotic areas |

No correlation was seen between the number of bacteria and the type of exudate, although this gas as a whole showed a small number of bacteria.

Table II gives the summary of findings for methyldichlorarsine in a few typical cases.

*3. Lewisite.*—A leucocytic exudate prevails in lewisite lungs. In practically all acute deaths leucocytes are predominant with epithelial cells and mononuclears present in much smaller numbers.

Of twenty-seven cases, seventeen showed a few bacteria, three

showed no bacteria, seven had many. No cases showed large numbers of bacteria. The lungs from this series showed fewer bacteria than any other.

*4. Phosgene.*—The first lesion in phosgene poisoning, and the one from which death usually occurs, is edema. If survival is prolonged

TABLE II

*Results Showing Number of Bacteria in a Few Typical Methyldichlorarsine Lungs*

| General condition of lungs | Pneumonic exudate | Bacteria |
|---|---|---|
| Congestion<br>Hemorrhage | Scattered leucocytes<br>Epithelial cells<br>Red blood cells | Few |
| Edema<br>Hemorrhage | Red blood cells<br>Leucocytes | Few, chiefly near bronchi |
| Hemorrhage<br>Atelectasis<br>Fibrin | Swollen epithelial cells | Few |
| Edema | Epithelial cells<br>Mononuclears | Very few |
| Congestion | Leucocytes<br>Few epithelial cells | Few<br>Some intracellular |
| Fibrin<br>Necrosis<br>Hemorrhage | Leucocytes<br>Few epithelial cells | Necrotic areas loaded with bacteria |
| Edema | Leucocytes<br>Mononuclears<br>Epithelial cells | Few<br>Some intracellular |

the edema fluid becomes infiltrated with leucocytes so that in the later deaths pneumonia is a common finding. The pneumonia is not peribronchial in character but is generalized throughout the alveoli as if arising from the alveolar walls. Leucocytes, mononuclears and epithelial cells are present. Most phosgene lungs in which an exudate was present, showed many bacteria.

### *B. Relation of Bacteria to Type of Exudate*

Desquamated epithelium is conspicuous in pneumonias due to irritating gases but in only a few cases does it form the entire exudate. Usually the picture is that of broncho-pneumonia, with epithelial cells, mononuclears and polymorphonuclear leucocytes composing the exudate. Frequently the leucocytes out-number the other cells.

The pneumonia of gassed lungs resembles the broncho-pneumonia seen in non-gassed lungs. Sometimes it is peribronchial in type, sometimes it involves a lobule uniformly. Hemorrhage, atelectasis and perivascular and peribronchial edema are typical findings in gassed lungs.

A glance at Table III shows that bacteria are prevalent in all types of pneumonic exudates found in gassed lungs.

TABLE III

*Results Showing Relation of Bacteria to Type of Exudate*

| Type of exudate | Few bacteria | Many bacteria | Large numbers |
|---|---|---|---|
| Leucocytes predominating | 50% | 30% | 20% |
| Epithelial cells predominating | 33% | 47% | 20% |
| Leucocytes and epithelial cells in equal numbers | 54% | 38% | 8% |

### *C. The Temperature of the Animal*

As a general rule gassed dogs do not run noticeably high temperatures. This would seem to indicate an absence of bacterial infection, but the inference cannot be drawn, as no information is at hand as to what temperature dogs show when infection is known to be present. A dog's temperature varies so markedly from day to day and from hour to hour that it does not appear to be an index of the animal's condition.

The highest temperature seen in the series studied was 106.2°F. The exudate in this animal was purely leucocytic, but very few bacteria were found. Another dog with a temperature of 106°F., showed necrosis of the lungs and large numbers of bacteria. In a dog showing a temperature of 104.2°F., the exudate was leucocytic and many

bacteria were present, but on the other hand, in several cases showing many bacteria, the temperature was normal.

### *D. The Length of Time Between Death and Autopsy*

There does not appear to be any relation between the time elapsing after death and the number of bacteria. Some of the cases showing the largest number of bacteria were autopsied very soon after death and some cases showing very few bacteria had been kept as long as 18 hours before autopsy was performed.

TABLE IV

*Results Showing Number of Bacteria in Lungs of Dogs Surviving Varying Lengths of Time after Gassing*

| Hours of survival | No. of cases | Lungs | Bacteria |
|---|---|---|---|
| Less than 12 | 5 | No exudate | Few |
| 12 | 1 | Leucocytes present | Few |
| 12–24 | 6 | Leucocytes and epithelium | Few 4, many 1, some 1 |
| 24–36 | 5 | Leucocytes | Few 3, none 2 |
| 36–48 | 4 | Leucocytes | Few 3, many 1 |
| 48–72 | 14 | Leucocytes | Few 6, many 8 |
| 72–96 | 5 | Leucocytes, 2 necrosis | Few 2, many intracellular 3 |
| 120 | 4 | Leucocytes, 1 necrosis | Many 4, intracellular |
| 140 | 5 | Leucocytes, 2 necrosis | 1 Few, 4 many |
| 9 days | 1 | Necrosis | Many, intracellular |
| 22 days | 1 | Leucocytes | Very many |
| 9 weeks | 1 | Chronic exudate | None |

The temperature at which the body was kept after death undoubtedly had more effect on the number of bacteria in the lungs, than did the length of time between death and autopsy.

No record of temperature is available but in view of the well preserved state of the cells it may be assumed that post-mortem degeneration was slight.

### *E. The Survival after Gassing*

If the bacteria found in the lungs are present in a causal relationship, it would be expected that the early deaths from pneumonia would

show as many bacteria as the later deaths, or at least that bacteria would be present in considerable numbers in the early deaths. If the presence of the bacteria is merely casual, and due to the injured lungs offering a favorable field for growth, the number might be expected to be smaller in the early deaths and to show an increase as the time of survival is longer.

The cases were grouped and studied therefore with regard to the number of hours of survival (Table IV).

Animals dying in less than 12 hours showed no exudate in the alveoli but a bronchial exudate was frequently present. At 12 hours there was one case of well-developed pneumonia, and above 12 hours most cases showed pneumonia. Areas of necrosis were not observed

TABLE V

*Summary of Table IV*

| Hours of survival | No. of cases | Bacteria |
|---|---|---|
| Less than 48 hours | 21 | None 2, few 16, many 3 |
| 48–72 hours | 14 | Few 6, many 8 |
| 72 hours–9 weeks | 17 | Few 3, many 14, many intracellular |

in deaths below 72 hours. Above that they were frequent. Above 72 hours many of the bacteria were observed to be engulfed by the leucocytes. Below 72 hours very few intracellular bacteria were seen.

Tables IV and V show that there were more bacteria in the lungs of animals surviving 48 hours or longer, than in those of animals dying at shorter periods of time after gassing.

### *F. Bacteria in Non-Gassed Lungs*

*1. In Normal Lungs.*—Cultures made from the trachea and bronchi of normal dogs showed plentiful growth. From the lung tissues in most cases there was no growth. Sections of normal lungs stained for bacteria showed a few bacteria on the bronchial mucosa but none in the alveolar structure.

*2. In Cases of Experimentally Produced Pneumonia.*—Pneumonia

TABLE VI

*Results Showing Bacteria Present in Pneumonias Produced by the Inhalation or Injection of Irritating Substances Other than War Gases*

| Animal | Substance | Method | Death | Condition of lungs | Bacteria | |
|---|---|---|---|---|---|---|
| | | | | | Culture | Stain |
| Dog 5 | $N_2O_2$ | Inhalation | Killed, $MgSO_4$ | Edema widespread. Exudate of leucocytes, fibrin, red cells | Diplococci | Occasional diplococcus. Few in edema fluid |
| Rabbit 16 | $CuSO_4$ (1% solution) | Intratracheally 1 cc. | Killed | Normal | None | |
| Rabbit 15 | $CuSO_4$ (1% solution) | Intratracheally 1 cc. | Died 11 days | Purulent pleurisy consolidation all lobes | Many colonies | Diplococci |
| Dog 35-82 | $CuSO_4$ (2% solution) | Intratracheally 4 cc. | Died 2 days | Necrosis of trachea, mediastinum and pericardium. Congestion of lungs | Many colonies | Diplococci |
| Dog 35-83 | $CuSO_4$ (2% solution) | Intratracheally 6 cc. | Died 2 days | Edema around trachea and mediastinum and pericardium, necrosis of tracheal mucosa and hemorrhage, edema, consolidation of lungs | Several colonies | Staphylococci, rods |
| Dog 35-92 | $CuSO_4$ (1.5% solution) | Intratracheally 6 cc. | Died 1 day | Edema | No growth. Few colonies from bronchi | Diplococci |
| Dog 35-93 | $CuSO_4$ (1.5% solution) | Intratracheally 5 cc. | Killed 2 days | Congestion, hemorrhage consolidation of lungs | Few colonies | Very minute rods |
| Dog 35-86 | Ethylbromacetate | Intravenously | Died 2 days | Hemorrhage, atelectasis, consolidation of lungs | Few colonies | Diplococci |

was induced in animals by the inhalation or injection of irritating substances, in order to compare the condition caused with that of gassed lungs. Table VI shows the results. Pneumonia was produced by the inhalation of nitric oxide fumes, by the intratracheal injection

TABLE VII

*Results Showing Relation of Bacteria to Exudate in Dogs Dying with Spontaneously Developed Pneumonia*

| Animal | Death | Condition of lungs | Bacteria | |
|---|---|---|---|---|
| | | | Cultures | Stain |
| Dog 6 | Killed, $MgSO_4$ | Consolidation of lungs. Enormous hypertrophy of bronchial mucosa. Bronchial exudate, glands dilated. Alveolar walls thick | Colonies from all lobes | Rods and staphylococci |
| Dog 7 | Died | Consolidation of lungs. Edema. Exudate of epithelial cells, mononuclears, few leucocytes | | Staphylococci, few diplococci |
| Dog 9 | Died | Consolidation of lungs. Exudate of leucocytes | | Large numbers of bacteria, intracellular |
| Dog 10 | Died | Consolidation all lobes. Exudate of leucocytes and mononuclears | | Many bacteria, most of them intracellular |
| Dog 11 | Died | Consolidation all lobes. Exudate of leucocytes, mononuclears and epithelial cells | | Many bacteria, intracellular |
| Dog 12 | Died | Consolidation all lobes. Exudate of leucocytes and epithelial cells | | Some bacteria, mainly intracellular |
| Dog 13 | Died | Consolidation all lobes. Edema. Exudate of leucocytes, mononuclears and epithelial cells | | Many bacteria, intracellular |

of copper sulfate solution, and by the intravenous injection of ethylbromacetate. None of these pneumonias were sterile.

*3. Pneumonia Occurring Spontaneously in Dogs.*—A number of dogs ng in the kennels were autopsied and found to have consolidation the lungs. These animals had not been gassed at any time. A few were killed with an injection into the heart of concentrated magnesium sulfate solution, when seen to be in bad condition.

The findings in this series are given in Table VII.

In a number of these animals the pneumonic exudate consisted largely of desquamated epithelial cells—the "desquamative pneumonia" of Buhl (13), Fraenkel (14) and Galdi (15), or the "chemical pneumonia" of other authors. That the anatomical picture, which Wood (2) claims is often produced by chemical agents without the aid of bacteria, can be produced by bacteria alone, is here clearly demonstrated. Furthermore, Galdi (15) has described similar pneumonias in which the infection occurred by the hematogenous route as a sequel to ulcerative endocarditis.

## V. CONCLUSIONS

The question of a causal relation of the bacteria in gassed lungs to the pneumonia present cannot be regarded as decided. It may be said that:

1. The appearance of gassed lungs with pneumonia is very similar to the pneumonia of known bacterial origin.
2. In a few cases the type of pneumonia found coincides with the reported cases of so-called "chemical pneumonia," which is characterized by a preponderance of epithelial cells in the exudate.
3. Gassed lungs are not sterile but show highly varying numbers of bacteria.
4. The bacteria are not intracellular and are not present in large numbers in the majority of cases.

The arguments for and against a causal relationship between the bacteria and the pneumonia may be summed up as follows:

### *1. Against a Causal Relationship*

*a*. The early appearance of pneumonia after gassing.

*b*. The occurrence of pneumonia with very small numbers of bacteria present.

*c*. The fact that very few bacteria are engulfed by leucocytes in gassed lungs, whereas large numbers are present in the non-gassed pneumonias and are conspicuously intracellular.

### 2. *In Favor of a Causal Relationship*

*a*. The presence of bacteria in any numbers.

*b*. The picture of broncho-pneumonia presented is similar to broncho-pneumonia of known bacterial origin.

*c*. Pneumonias characterized by large numbers of epithelial cells in the exudate (so-called "chemical pneumonia") occur in animals that were never gassed or subjected to other irritating substances in any way.

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## EXPLANATION OF PLATES

### PLATE 4

FIG. 1. Desquamative pneumonia from lung of dog gassed with phosgene. Symptoms disappeared in 2 days. Killed 1 week later.

FIG. 2. Patch of desquamative pneumonia in a dog that recovered from mustard gassing and was killed 9 months after recovery.

### PLATE 5

FIG. 3. Desquamative pneumonia in a dog that was never gassed or exposed to irritating substances of any kind. Killed because it was thought he had worms. Positive culture and bacterial stain from lungs.

FIG. 4. Nitric oxide pneumonia—2 days—leucocytic type.

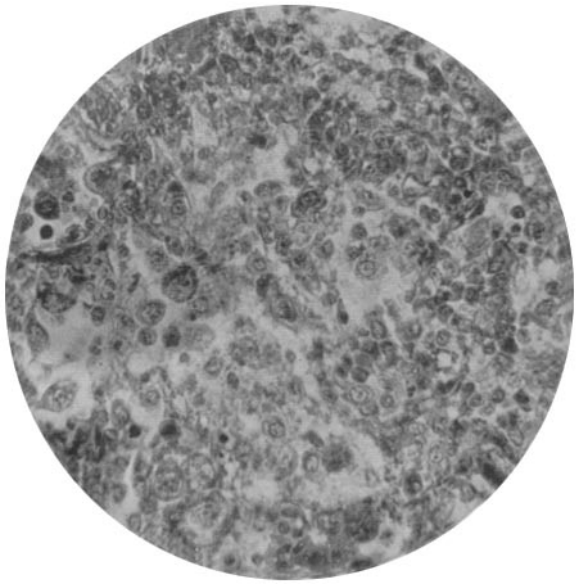

FIG. 1

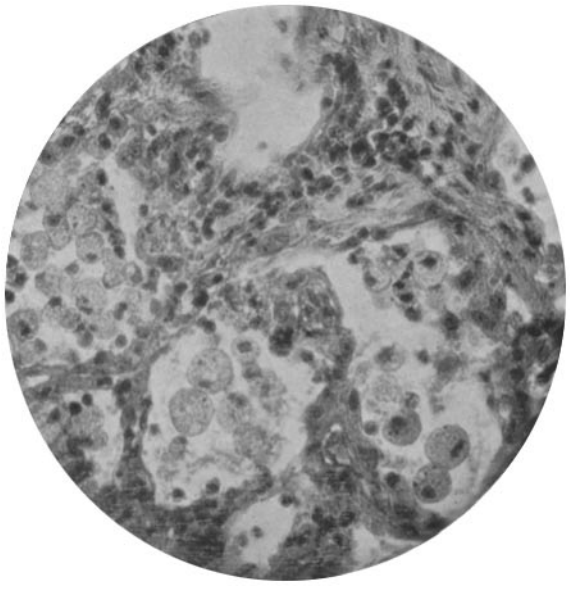

FIG. 2

(Koontz and Allen: Relation of bacteria to "chemical pneumonia")

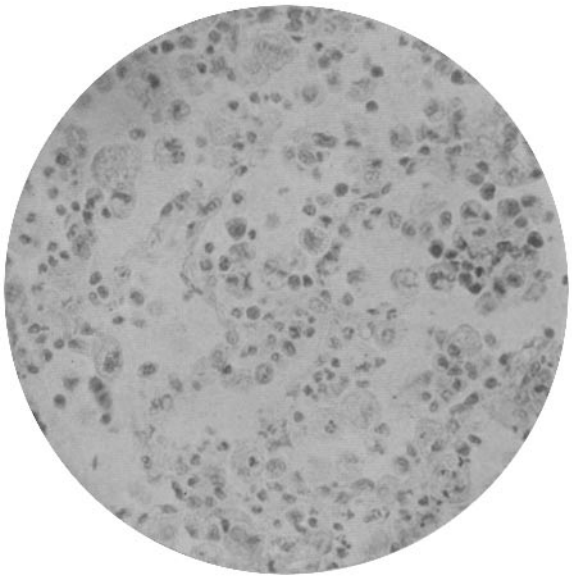

FIG. 3

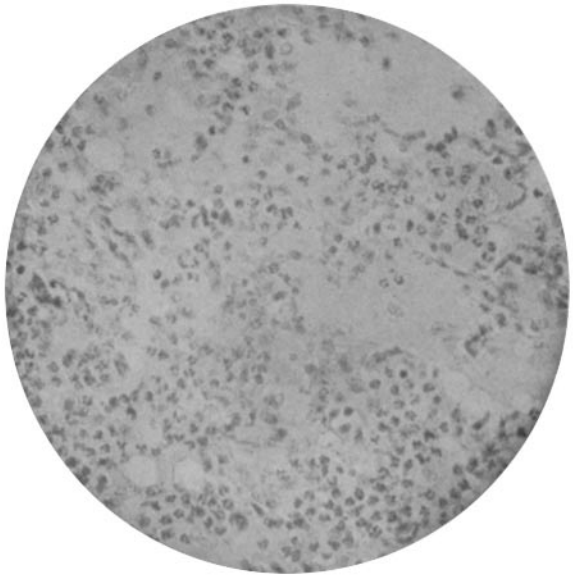

FIG. 4

(Koontz and Allen: Relation of bacteria to "chemical pneumonia")