

## OBSERVATIONS ON BLOOD REACTION IN EXPERIMENTAL PNEUMONIA.\*

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It has been previously reported (1) that we succeeded in obtaining experimental pneumonia in 46 of a series of 60 dogs inoculated by tracheal insufflation with various organisms. Of these 46, eight died within 18 hours of inoculation, and two were inadequately observed, so that satisfactory data were obtained from 36. Detailed results on six of these, inoculated with *Bacillus mucosus capsulatus*, were presented (1), in which erythrocyte counts, blood volume, hemoglobin, and hematocrit determinations revealed an actual loss of circulating erythrocytes, without compensatory regeneration, during the course of the pneumonic process.

It is the purpose of the present paper to report certain data obtained from the remaining 30 of the successfully observed animals. This number includes eight inoculated with *Bacillus bronchisepticus*, one with *Streptococcus hæmolyticus*, one with *Streptococcus viridans*, one with *Bacillus influenzae*, and nineteen with *Bacillus mucosus capsulatus*. In these animals, lung lesions were followed by fluoroscopic and x-ray examinations; lung ventilation was recorded, when the dogs were not too large, by means of a body plethysmograph, and 20 cc. of blood, on the average, were drawn for the various blood determinations. Data were secured daily in these ways until death or recovery of the animals took place.

The blood was drawn from the femoral artery into an oxalated syringe through the intact skin, with suitable aseptic precautions and measures to prevent hemorrhage. Determinations of the alkaline

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reserve and of the total acetone bodies were made on most of the dogs by essentially the methods introduced by Van Slyke, Cullen, and Fitz (2-4). In four we followed the oxygen content of arterial and venous blood, using Van Slyke's technique (5), and in five animals we studied the carbon dioxide content of arterial blood by the method of Van Slyke and Stadie (6). In these five dogs, we also made electrometric measurements of the pH of the arterial blood. In five other dogs, quantitative estimations were made of the urea and ammonia content of the urine and qualitative tests were made for the presence in the urine of albumin, sugar, acetone, and diacetic acid. Whenever blood was used for gasometric determinations, it was drawn out of contact with air, and transferred immediately under oil to the instruments in which the measurements were made. Except for the acetone bodies, determinations were made in duplicate.

#### RESULTS.

In Table I data are submitted showing the effects of the pneumonia produced by the various organisms on the lung ventilation, alkaline reserve, acetone bodies, and erythrocyte and leucocyte counts, in typical animals selected from the series. In Table II results may be found for two dogs inoculated with *Bacillus bronchisepticus*, and two with *Bacillus mucosus capsulatus*, with respect to lung ventilation, alkaline reserve, acetone bodies, and oxygen content of arterial and venous blood. Table III presents the significant figures on lung ventilation, acetone bodies, carbon dioxide content of arterial blood, and the hydron concentration of arterial blood in five dogs inoculated with *Bacillus mucosus capsulatus*. Finally, the urine findings, together with data on the alkaline reserve, in three typical animals inoculated with *Bacillus mucosus capsulatus*, may be seen in Table IV. Detailed results are presented, therefore, on eighteen of the thirty animals. The findings on the twelve animals omitted from the tables closely parallel the data shown, according as to whether death or recovery took place, but the estimations on the various functions were not as complete as in the case of those included in the tables.

The results varied with the virulence of the infection, and with the extent and duration of the pulmonary involvement. As was noted previously (1), the most constant finding was a reduction in the

TABLE I.  
*Data upon Lung Ventilation, Alkaline Reserve, Acetone Bodies, Erythrocytes, and Leucocytes, in Dogs with Experimental Pneumonia.*

| Dog No.   | Date.           | Lung ventilation per min. | Alkaline reserve. | Acetone bodies per liter. | Erythrocytes per c.mm. | Leucocytes per c.mm. | Organism; x-ray findings; remarks.    |                                       |
|-----------|-----------------|---------------------------|-------------------|---------------------------|------------------------|----------------------|---------------------------------------|---------------------------------------|
|           | 1920            | cc.                       | vol. per cent     | mg.                       | million                | thousands            |                                       |                                       |
| 4         | Oct. 6          | 3,818                     | 40.1              | 36.2                      | 6.4                    | 8.2                  | <i>B. bronchisepticus.</i> Pulse 156. |                                       |
|           | " 8             | 4,967                     | 41.4              | 25.8                      | 6.2                    | 37.5                 | Right middle lobe diffuse. Pulse 190. |                                       |
|           | " 11            | 7,918                     | 41.2              | 90.6                      | 5.4                    | 38.8                 | Entire right lung dense. Pulse 150.   |                                       |
|           | " 12            | 2,513                     | 37.6              | 178.1                     | 5.4                    | 40.2                 | Right lung dense. Pulse 156.          |                                       |
|           | " 14            | 2,378                     | 39.8              | 160.2                     | 5.1                    | 21.8                 | Right lung diffuse. Pulse 150.        |                                       |
| Recovery. | " 18            | 3,689                     | 40.2              | 76.3                      | 5.6                    | 18.1                 | Right middle lobe diffuse. Pulse 130. |                                       |
| 6         | " 18            | 6,361                     | 46.4              | 53.1                      | 6.6                    | 9.3                  | <i>B. bronchisepticus.</i>            |                                       |
|           | " 20            | 4,783                     | 39.2              | 88.3                      | 5.2                    | 19.6                 | Right lung diffuse.                   |                                       |
|           | " 22            | 5,135                     | 33.8              | 75.8                      | 4.4                    | 32.2                 | " " dense; lower left diffuse.        |                                       |
|           | " 25            | 4,520                     | 47.4              | 66.9                      | 3.6                    | 51.0                 | Both lungs dense.                     |                                       |
|           | Death.          | " 27                      |                   | 31.2                      | 188.4                  |                      | 78.4                                  | Marked lipemia.                       |
| 12        | Nov. 16         | 2,861                     | 42.1              | 21.7                      | 6.4                    | 16.2                 | <i>B. bronchisepticus.</i>            |                                       |
|           | " 17            | 2,720                     | 53.2              | 48.6                      | 6.2                    | 33.4                 | Right middle dense.                   |                                       |
|           | " 19            | 6,050                     | 46.9              | 35.2                      | 5.6                    | 30.4                 | Left upper diffuse.                   |                                       |
|           | " 21            | 2,639                     | 46.1              | 24.3                      | 5.8                    | 27.2                 | Right middle "                        |                                       |
|           | Recovery.       | " 23                      | 3,028             | 46.3                      | 37.0                   | 5.1                  | 26.0                                  | Both lungs clear.                     |
| 16        | Dec. 21         | 2,025                     | 45.4              | 33.5                      | 5.8                    | 14.3                 | <i>Streptococcus hemolyticus.</i>     |                                       |
|           | Recovery.       | " 23                      | 2,816             | 43.0                      | 53.2                   | 5.2                  | 31.0                                  | Right middle diffuse.                 |
| 20        | 1921<br>Jan. 10 | 6,038                     | 46.8              | 15.3                      | 8.7                    | 10.1                 | <i>Streptococcus viridans.</i>        |                                       |
|           | " 12            | 5,107                     | 43.5              | 44.6                      | 5.6                    | 29.8                 | Both upper lobes dense.               |                                       |
|           | Recovery.       | " 14                      | 5,430             | 51.4                      | 65.0                   | 6.8                  | 17.2                                  | Right middle diffuse.                 |
|           | 22              | " 18                      | 2,680             | 55.0                      | 23.0                   | 6.4                  | 18.2                                  | <i>B. influenza.</i>                  |
| " 20      |                 | 4,702                     | 42.3              | 67.1                      | 4.9                    | 36.1                 | Right lower diffuse.                  |                                       |
| " 22      |                 | 1,124                     | 42.8              | 88.9                      | 4.8                    | 42.4                 | Entire right " left upper dense.      |                                       |
| Recovery. |                 | " 25                      | 3,122             | 50.1                      | 43.0                   | 6.0                  | 46.5                                  | Right lung clear; left upper diffuse. |

number of circulating erythrocytes, which occurred in all animals, but most noticeably in those in which the pneumonia was severe and of long duration. In most cases there was an increase in lung ventilation during the first few days of the disease, which was followed

TABLE II.

*Data upon Lung, Ventilation, Alkaline Reserve, Acetone Bodies, and Oxygen Content of Arterial and Venous Blood in Experimental Pneumonia.*

| Dog No. | Date.          | Lung ventilation per min. | Alkaline reserve. | Acetone bodies per liter. | Oxygen.       |               | Organism; x-ray findings; remarks.  |
|---------|----------------|---------------------------|-------------------|---------------------------|---------------|---------------|---|
|         |                |                           |                   |                           | Arterial      | Venous        |   |
|         |                | cc.                       | vol. per cent     | mg.                       | vol. per cent | vol. per cent |   |
| 8       | 1920 Nov. 3    | 5,249                     | 43.0              | 19.2                      | 24.2          | 18.4          | <i>B. bronchisepticus.</i><br>Right lung dense.<br>" " very dense;<br>left upper dense.   |
|         | " 6            | 4,920                     | 39.0              | 68.5                      | 16.8          | 12.3          |   |
|         | Death. " 7     | 2,909                     |                   | 121.7                     |               |               |   |
| 9       | " 6            | 3,866                     | 43.6              | 29.7                      | 22.3          | 17.5          | <i>B. bronchisepticus.</i><br>Left lower diffuse; right upper diffuse.<br>Entire left dense.<br>Left dense; right diffuse.<br>" lung diffuse.<br>Lungs clear. |
|         | " 8            | 5,975                     | 50.9              | 32.3                      | 18.4          | 12.0          |   |
|         | " 9            | 3,138                     | 44.8              |                           |               |               |   |
|         | " 10           | 2,614                     | 33.7              | 167.0                     | 15.3          | 9.9           |   |
|         | Recovery. " 12 | 4,017                     | 46.5              | 28.1                      | 16.5          | 9.4           |   |
|         | " 15           | 4,112                     | 47.2              | 11.5                      | 16.4          | 12.2          |   |
|         |                | Respirations per min.     |                   |                           |               |               |   |
| 15      | Dec. 8         | 20                        | 41.8              | 32.6                      | 19.6          | 14.8          | <i>B. mucosus capsulatus.</i><br>Right lung dense.<br>Lungs clear.  |
|         | " 10           | 40                        | 32.4              | 103.1                     | 17.5          | 12.3          |   |
|         | Recovery. " 13 | 60                        | 42.3              | 60.4                      | 17.4          | 10.3          |   |
| 29      | 1921 Feb. 11   | 20                        | 50.8              | 46.3                      | 20.7          | 15.6          | <i>B. mucosus capsulatus.</i><br>Left lung diffuse.<br>" dense; right upper diffuse.  |
|         | " 12           | 32                        | 49.0              | 44.8                      | 19.7          | 12.8          |   |
|         | Death. " 13    | 16                        | 39.5              | 133.6                     | 15.2          | 9.0           |   |

by a marked decrease in many instances in which the lung lesions were severe and widespread. If recovery took place, the lung ventilation returned to normal or went above normal, as the lungs cleared. In the acute and fatal cases, the respiratory activity was usually markedly diminished.

The alkaline reserve showed significant loss only in the most severe or fatal cases. There often appeared to be a mobilization of alkali in the blood during the first few days following inoculation, which in one instance (No. 12) was marked and continued during the course of the infection. A lowering of the alkaline reserve due to increased

TABLE III.

*Data upon Lung Ventilation, CO<sub>2</sub> Content and pH of Arterial Blood, Acetone Bodies, and Erythrocytes in Dogs Inoculated with B. mucosus capsulatus.*

| Dog No.   | Date.   | Lung ventilation per min. | Arterial CO <sub>2</sub> . | pH   | Acetone bodies per liter. | Erythrocytes per c.mm. | Organism; x-ray findings; remarks.       |
|-----------|---------|---------------------------|----------------------------|------|---------------------------|------------------------|--|
|           | 1921    | cc.                       | vol. per cent              |      | mg.                       | million                |  |
| 31        | Feb. 15 | 4,300                     | 51.3                       | 7.41 | 68.0                      | 7.2                    |  |
| Death.    | " 17    | 3,220                     | 48.7                       | 7.33 | 93.6                      | 6.0                    | Entire left dense.                       |
| 32        | " 18    | 3,100                     | 43.5                       | 7.46 | 37.2                      | 6.8                    |  |
| Death.    | " 20    | 2,850                     | 38.7                       | 7.32 | 89.3                      | 5.6                    | Entire left and right middle dense.      |
| 35        | " 23    | 3,320                     | 57.5                       | 7.52 | 18.2                      | 7.8                    |  |
|           | " 25    | 4,610                     | 42.4                       | 7.42 | 40.1                      | 6.9                    | Entire left and right upper diffuse.     |
| Recovery. | " 26    | 3,180                     | 43.2                       | 7.42 | 42.6                      | 6.8                    | Left lower diffuse.                      |
| 37        | Mar. 1  | 2,530                     | 44.2                       | 7.43 | 38.6                      | 7.8                    |  |
|           | " 3     | 2,940                     | 38.8                       | 7.31 | 61.7                      | 6.2                    | Left upper dense.                        |
| Death.    | " 4     |                           | 36.4                       | 7.25 | 102.4                     | 6.0                    |  |
| 38        | " 2     | 2,280                     | 40.4                       | 7.47 | 26.5                      | 7.2                    |  |
|           | " 4     | 3,070                     | 38.2                       | 7.39 | 53.8                      | 6.6                    | Left lower dense; right middle diffuse.  |
| Death.    | " 5     | 1,720                     | 24.1                       | 7.22 | 122.3                     | 6.0                    | Entire left dense; entire right diffuse. |

pulmonary activity, according to the acapnial process as outlined by Henderson and Haggard (7), was noted in four animals (Nos. 16, 22, 35, and 38). The significantly low levels of alkaline reserve, however, usually coincided with high levels of acetone bodies. The acetone bodies generally increased when lung ventilation was reduced,

and when the pulmonary involvement was most severe. In light cases, as in No. 12, the changes in the acetone bodies were relatively insignificant.

Arterial and venous oxygen diminished as the infection followed inoculation, and if recovery took place, the values tended to return gradually to the normal. The diminution was in relatively the same proportions for arterial and venous blood, within the limits of error, so that it is doubtful if any marked change took place in the rate of oxygen consumption. The tendency of the figures indicates, however, a slight increase. We made no determinations of oxygen capacity,

TABLE IV.

*Data upon Alkaline Reserve, Quantitative Urea and Ammonia, and Qualitative Albumin, Sugar, Acetone, and Diacetic Acid, in Experimental Pneumonia.*

| Dog No. | Date.   | Alkaline reserve.    | Urea per 24 hrs. | Ammonia per 24 hrs. | Albumin. | Sugar. | Acetone. | Diacetic acid. |
|---------|---------|----------------------|------------------|---------------------|----------|--------|----------|----------------|
|         | 1921    | <i>vol. per cent</i> | <i>gm.</i>       | <i>gm.</i>          |          |        |          |                |
| 41      | May 20  | 42.3                 | 0.252            | 0.102               | —        | —      | —        | —              |
|         | " 22    | 38.6                 | 0.421            | 0.232               | +        | —      | —        | —              |
| Death.  | " 24    | 33.2                 | 0.529            | 0.308               | +        | —      | +        | —              |
| 43      | July 12 | 46.1                 | 0.305            | 0.127               | —        | —      | —        | —              |
| Death.  | " 13    | 34.0                 | 1.340            | 0.572               | +        | —      | ?        | ?              |
| 44      | " 14    | 47.3                 | 0.210            | 0.085               | —        | —      | —        | —              |
| Death.  | " 15    | 38.8                 | 1.440            | 0.408               | +        | —      | ?        | —              |

so that no conclusions can be drawn from our figures regarding the oxygen unsaturation of arterial or venous blood.

The hydrion concentration of arterial blood, as indicated by pH, rose after the inoculations, the most marked increases being noted in the fatal and prolonged cases.

The daily urea and ammonia output showed a considerable rise after inoculation. Albumin was noted in the urine in all cases examined, and it appeared continuously during the course of the infection. Sugar was not found at any time. Acetone was definitely noted in the urine in only one instance, while diacetic acid was absent except in one doubtful case.

## DISCUSSION.

An explanation of these changes in the blood and urine in experimental pneumonia may be offered on the basis of reduced oxidation. The anoxemia in pneumonia is of both the anoxic type, as defined by Barcroft (8), due to the pulmonary congestion in the lungs, and of the anemic type, as evidenced by the reduction in erythrocytes and hemoglobin (1). By interfering with normal oxidative processes in the body, the pneumonic anoxemia may lead to an increased pulmonary ventilation, with blowing off of carbon dioxide, and a consequent disturbance in the acid-base relationship, or if the respiratory mechanism cannot meet the emergency, to an accumulation of fixed acids in the blood with a resulting acidosis.

These experimental observations confirm many clinical reports.

Peabody (9) noted a decrease in the carbon dioxide of blood in lobar pneumonia, and Palmer and Henderson (10) found that during the fastigium of pneumonia larger amounts of sodium bicarbonate by mouth were necessary to lower urine acidity than was the case in normal conditions. Lewis (11) reported that the blood of pneumonic patients had a diminished affinity for oxygen, which is characteristic of acidosis. Palmer (12) found that a large amount of organic acid, free at a pH of 5.0, was excreted in the urine of cases of acute lobar pneumonia, but that the acidosis, as indicated by the combined carbon dioxide in the plasma, was seldom severe. Barach, Means, and Woodwell (13) observed that the available blood alkali in pneumonia, as shown by the level of the carbon dioxide dissociation curve, tended to be lower than the normal. It was reported by Killian (14) that about the time of the crisis in pneumonia of various types, there was an increase in the non-protein nitrogen, uric acid, urea, and creatinine in the blood, with a decrease in the chlorides and carbon dioxide-combining power.

Our experimental findings also lend support to the rationale of the oxygen and alkali therapy in pneumonia as developed by Barach and Woodwell (15) and by Means and Barach (16), and of the oxygen chamber treatment of pneumonia as introduced by Stadie (17). It was suggested by Barach, Means, and Woodwell (13) that when an acidosis was present in pneumonia patients, either in the sense of a low level of available blood alkali or a diminished blood pH or a combination of the two, the administration of sodium bicarbonate might help to reduce the work of the respiratory system. It was pointed out that the use of the alkali should be carefully controlled in order

to avoid an alkalosis, and that when anoxemia is present, oxygen therapy should also be used. It would seem from our data that a possible acidosis in pneumonia would be dependent upon a developing anoxemia, and that the alleviation of this should be the first consideration.

It has been stated by Barach (18) that: "The disease in which acute anoxemia occurs with the greatest frequency and with the greatest severity is pneumonia." Our study has indicated the rapidity and severity with which this anoxemia may be produced under experimental conditions. It is possible roughly to correlate our indications of developing acidosis with the severity of the pulmonary development as revealed by x-ray examinations, but with the exception of the rapidly fatal cases, almost the same correlation may be made with the severity of the anemia. It is more likely, however, that the acidosis of pneumonia is due chiefly to the anoxic anoxemia, and that the anemic anoxemia secondarily contributes to its development. Light might be shed upon this question by determining the oxygen capacity of arterial blood during the course of experimental pneumonia. Unfortunately, we made no such determinations, but the evidence from clinical studies does not indicate that the anemic anoxemia is of very great importance in the development of the acidosis of pneumonia.

There is no evidence from our figures that the anoxemia encountered in pneumonia may be of the stagnant type. This agrees with the report made by Stadie (19) on the patients studied by him, in which the oxygen consumption remained within normal limits, indicating that the cardiac output had not been diminished. In these clinical cases, Stadie (19) found no unusually low oxygen capacities for the blood, but a tendency for an increased arterial and venous oxygen unsaturation. An arterial unsaturation of more than 20 per cent was usually associated with a fatal outcome. These findings indicate that the anoxic anoxemia in pneumonia is relatively far more marked than the anemic anoxemia.

#### SUMMARY.

The correlation of the lung lesions and anemia in dogs suffering from experimental pneumonia induced by various organisms, with



changes in the respiratory activity and in the acid-base relationship in blood, indicates that the developing acidosis, most marked in the severe cases, is due chiefly to the effects of an anoxic anoxemia.

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