Observations on the Pathogenesis of the Pneumonitis Associated with Severe Infections in Other Parts of the Body

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RESPIRATORY insufficiency has become recognized as a frequent complication and often the cause of death in patients who have suffered from shock, severe trauma, and sepsis. Burke [7] *et al.*,[2, 6] as well as ourselves [12] have emphasized the importance of pulmonary complications in determining the course of survival or death in fulminating peritonitis. Others [15] have demonstrated the same thing in burns. More recently, the importance of pneumonitis as a cause of postoperative death has been emphasized by the incidence of "wet lung" among the wounded in Viet Nam who were resuscitated and survived the necessary surgical procedures.[13]

The frequent atelectasis, pneumonitis, and pulmonary abscesses accompanying peritonitis, burns, and other forms of severe nonthoracic sepsis was assumed to be due to inadequate respiratory exchange and inefficient clearance of pulmonary secretions. On the other hand, Moon [29] demonstrated a pattern of pulmonary congestion and inflammatory response common to many of these conditions. It is difficult to be certain of its significance or to arrive at a clear understanding of the pathogenesis of pneumonia from the study of histological sections obtained at postmortem. Inevitably agonal changes associated with circulatory failure or with the prolonged course of the disease prior to the patient's death render it impossible to determine how the process started and evolved.

To study respiratory, circulatory, and metabolic alterations associated with severe sepsis, it is important to develop standardized experimental models. Induced peritonitis incorporates many of the characteristic clinical features. These include: hypovolemia due to translocation of fluid [16] and the presence of toxic materials derived from bacteria and necrotic tissue.[17] Initially, cecal ligation was undertaken as a method of experimentally producing the peritonitis. The animals' response to this embodied many of the circulatory and metabolic patterns described in man including a period of reduced cardiac output, followed by a hyperdynamic state, and death if the output fell.[12, 41] On the third to fourth day a clinical pattern of hypoxia and respiratory alkalosis occurred prior to pulmonary and circulatory failure. However, it became apparent that frequently the lung and other tissues were being invaded by C. welchii. This type of pneumonitis was unacceptable in view of

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the destructive characteristics of these organisms which seldom are grown from the lungs of patients. To obviate this difficulty, penicillin in large doses was administered. Subsequently, no cultures of pulmonary parenchyma have contained clostridia.

To determine whether the early phase of hypovolemia or the presence of endotoxin and other circulating agents may be responsible for establishing the associated pneumonitis, two other series of experiments were undertaken and are presented. The first was a comparative study of the effects of hypovolemic shock on the lungs which confirms descriptions in the literature.[18, 22, 40] In the second, following the suggestion of Pulaski,[35] a suspension of coliform bacilli and bile were injected intraperitoneally employing a standardized dose of organisms according to body weight.

Measurements of blood gases, and circulatory responses were made in all groups to correlate with the histological observations and bacteriological examination of the lungs. Specimens for fixation were taken only from animals which were sacrificed to avoid morphologic or bacteriologic postmortem alterations. Therefore, this report deals only with the lungs, of surviving animals. It is not conceived of as a study of mortality or other bodily changes associated with sepsis except as they bear upon the etiology of pneumonitis.

Based upon these experiments and upon clinical observations, it is the purpose of this paper to demonstrate that the experimental models are a valid means for studying the pathogenesis of the pneumonitis associated with severe clinical sepsis. A concept is proposed that a common response of the lung exists which is related to an inflammatory reaction involving the septal capillaries to which both the low cardiac output and toxic agents contribute. Starting with red cell congestion, it passes through two other phases, monocytic phagocytosis with septal edema, progressing on to atelectasis or confluent pneumonia accompanied by polymorphonuclear leukocyte infiltration.

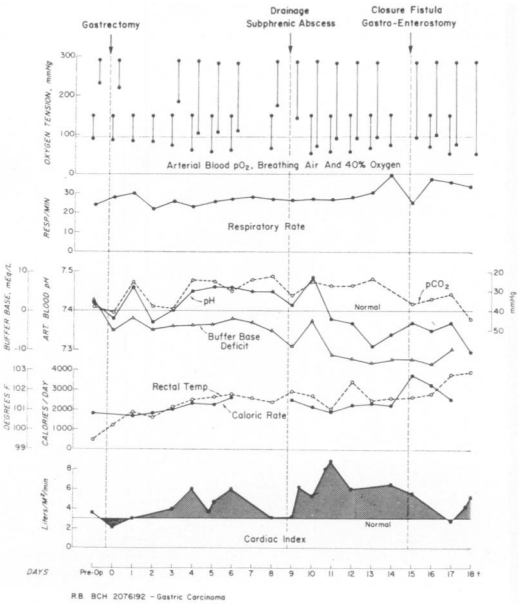

FIG. 1. An example of postoperative respiratory failure in patient who developed peritonitis and a fistula following a gastrectomy. Note the respiratory alkalosis accompanied by progressive decline of arterial oxygen tension when breathing both air and 40% oxygen. This is evidence of a "pulmonary shunt." For details, please see text.

Methods and Materials

With the exception of the measurements of caloric energy expenditure, the observations made in the patients studied and those in the animals, employed essentially the same methods. Cardiac output was determined by means of indocyanine green dye dilution curves employing a computer. Calculations from manual measurements of the recorded curves gave excellent linear agreement (±2.8%) with those obtained from the computers.* Pressures were recorded by Statham strain gauges connected to catheters placed into the right atrium and a peripheral artery. When not used, these were kept filled with a dilute solution of

* Supplied by the Gilford Co., Yellowsprings, Ohio, and the Lexington Instrument Co., Boston, Massachusetts.

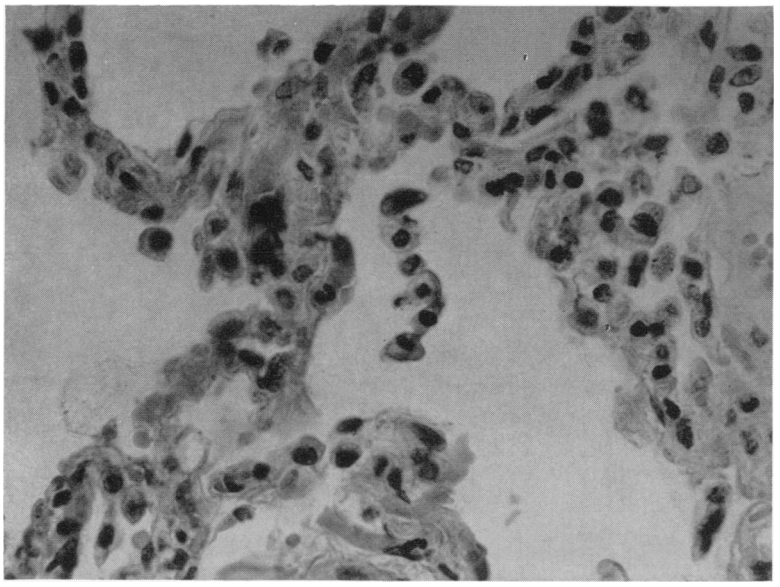

FIG. 2. Postmortem section of lung from patient presented in Fig. 1. This is representative of areas showing congested alveolar septa containing numerous large monocytes and red cells. Original magnification ×250.

heparin and saline. In certain animal preparations, needles were inserted into the pulmonary artery and left atrium through previously placed conduits for both pressure measurements and blood sampling. Blood pH and pCO_2, as well as buffer base values were measured by the method of Astrup [4] or by the Severinghaus electrode.* The blood oxygen tension was obtained using the Clark polarograph.*

The rate of caloric metabolic energy expenditures of patients was measured by the indirect method of Hardy and his associates.[43] This technic is based on the assumption that heat production equals heat loss (convective, radiant, and evaporative minus heat storage in the body). Average skin temperature and core temperature are measured by thermocouples placed at eight different locations of the body including the rectum. By comparing these with the ambient temperature, convective and radiant heat losses are estimated. Accurately measured weight loss employing the "metabolic bed" ** permitted a reasonably accurate estimate of evaporative heat loss.

* Manufactured by Instrumentation Laboratory, Inc., Watertown, Mass.

** Manufactured by the Brookline Instrument Co., White Plains, New York.

In an attempt to obtain meaningful bacteriological and histological observations on the lungs of the experimental animals, all dogs were rejected from the series which gave evidence of pre-existing rhinitis, cough, or fever over 102.5° F. rectal. No dogs or rats which died were used to obtain pulmonary specimens.

The animals were sacrificed rapidly by an overdose of Nembutal given intravenously. The chest was opened with full sterile precautions. An immediate assessment of the gross state of the lung, looking for atelectasis surface hemorrhages, and areas of consolidation was made. A sample of pulmonary parenchyma was obtained for culture, usually from both lungs. Clamps were placed across the area of biopsy. One lobe was inflated with 10% formalin solution for subsequent stain by Sudan B or Oil red O. The remainder of the lung was inflated with Teleshcnetzky's solution under no more than 15 cc. of water pressure. Samples were taken from two or more lobes for permanent sections, employing hematoxylin and eosin or Giemsa stains. An attempt was made to grade the state of the lung based upon gross appearance and the histological changes on a scale of I to IV. These included intra-alveolar hemor-

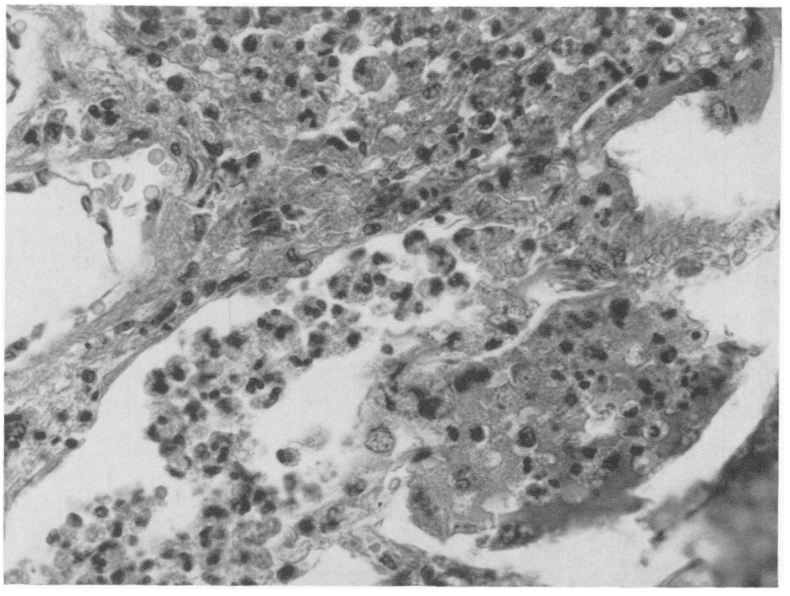

FIG. 3. Another representative section from lung of patient presented in Fig. 1. Note the numerous polymorphonuclear leukocytes both in the alveoli and in the alveolar septa. Original magnification ×250.

rhage, packing of the erythrocytes in the capillaries and the interstitial spaces of the septa, septal thickening and edema, the relative number of monocytic phagocytes and large monocytic cells present in the septa, focal alveolar collapse, focal atelectasis, the presence of polymorphonuclear leukocytes, the presence of consolidation or definitive abscesses.

Qualitative bacteriological studies included aerobic and anaerobic cultures of lung homogenate and peritoneal fluid in Trypticase soy broth and on blood agar plates.

Clinical Observations

In Figure 1 is shown the data obtained from a man who developed respiratory failure secondary to postoperative peritonitis. He was 46 years old, admitted for gastrectomy because of an unhealed ulcer of the greater curvature. Following an 80% subtotal gastrectomy, permanent sections disclosed the presence of gastric carcinoma extending in to the suture line. On the fourth day it became apparent that he was developing peritonitis as indicated by ileus and a rising temperature. The arterial blood oxygen tension while breathing air began to decline. When made to breathe a 40% oxygen mixture, the oxygen tension no longer rose to a value of 230 as it had prior to operation. On the fifth day the arterial oxygen tension while breathing air was 60 mg. Hg. At this time a respiratory alkalosis accompanied by an arterial blood pH of 7.46 developed. Simultaneously the body temperature, energy expenditure, and cardiac output all increased well above the normal resting values. The respiratory alkalosis was maintained throughout the remainder of his course until the last day just prior to death. On the ninth day a subphrenic abscess was drained. Thereafter, the respiratory situation deteriorated despite all precautions. A tracheostomy was performed, and the patient was given 40% oxygen. With this an oxygen tension of 90 mm. Hg could be maintained in the arterial blood. Because a fistula had developed at the drain site resulting in severe losses of gastric fluid, closure of the breakdown of the gastroenterostomy was attempted. However, the respiratory situation further deteriorated. Despite the use of a ventilator the oxygen tension fell to 48 mm. Hg on the 18th day.

At autopsy there were large areas of

TABLE 1. *Hemodynamic and Blood Gas Values: Controls and Experimental Peritonitis and Hypovolemic Shock*
(Average ± Standard Deviation)

A. Control Group: Laparotomy only (8 dogs)

	Preoperative	Day 0	Day 1	Day 2	Day 3	Day 4
Arterial blood pO_2	93.7 ± 6.7	87.3 ± 7.4	87.6 ± 7.7	85 ± 7.6	87 ± 3.1	88 ± 4.2
Arterial blood pH	7.41 ± .02	7.41 ± .02	7.41 ± .02	7.41 ± .01	7.42 ± .01	7.41 ± .02
Arterial blood pCO_2	34.5 ± 4.8	33.8 ± 2.8	33.7 ± 2.3	35.5 ± 3.4	33.8 ± 4.3	34.3 ± 4.3
Mean arterial blood pressure	129 ± 23	130 ± 24	130 ± 19	130 ± 18	124 ± 19	122 ± 18
Cardiac index	3.3 ± 0.3	3.5 ± 0.3	3.4 ± 0.3	3.2 ± 0.2	3.4 ± 0.2	3.4 ± 0.2

B. Survivors of Cecal Ligation (14 dogs)

	Preoperative	Day 1	Day 2	Day 3	Day 4	Day 5
Arterial blood pO_2	91.8 ± 1.2	86.0 ± 3.4	85.6 ± 2.8	79.5 ± 2.7	76.3 ± 1.7	80.7 ± 2.1
Arterial blood pH	7.40 ± 0.01	7.37 ± 0.01	7.42 ± 0.01	7.43 ± 0.01	7.45 ± 0.00	7.46 ± 0.01
Arterial blood pCO_2	36.9 ± 1.2	28.3 ± 1.5	32.1 ± 1.8	32.4 ± 2.4	30.1 ± 2.3	31.5 ± 2.0
Mean arterial blood pressure	115.5 ± 3.4	102.4 ± 4.6	102.1 ± 3.1	106.8 ± 5.1	100.4 ± 2.1	104.0 ± 4.5
Cardiac index (liter/m^2/min)	3.9 ± 0.3	3.2 ± 0.3	3.7 ± 0.2	3.9 ± 0.2	3.5 ± 0.2	4.2 ± 0.3

C. Hypovolemic Shock Survivors (7 dogs)

	Prebled	Hypovol. 2 hours	Shed Blood reinf. 1 hr.	Day 1	Day 2	Day 3
Arterial blood pO_2	87 ± 6	93 ± 9	89 ± 6	90 ± 4	89 ± 5	87 ± 7
Arterial blood pH	7.39 ± .02	7.32 ± 0.4	7.36 ± .04	7.39 ± .03	7.42 ± .02	7.42 ± .02
Arterial blood pCO_2	35.1 ± 2.1	23.1 ± 6.1	23.6 ± 3.5	28.5 ± 2.1	30.9 ± 2.4	32.1 ± 3.1
Mean arterial blood pressure	110 ± 10	43 ± 4	125 ± 11	103 ± 12	93 ± 12	112 ± 5
Cardiac index (liter/m^2/min.)	3.3 ± .9	1.2 ± .2	4.7 ± 1.2	3.6 ± .9	3.8 ± .7	3.5 ± .8

D. Survivors of Intraperitoneal Injection: E. Coli + Bile (26 dogs)

	Preoperative	Day 0 (4–8 hrs.)	Day 1	Day 2	Day 3
Arterial blood pO_2	90.0 ± 12.5	93.7 ± 6.0	88.3 ± 8.2	86.6 ± 8.5	85.5 ± 7.5
Arterial blood pH	7.420 ± 0.04	7.425 ± 0.04	7.404 ± 0.03	7.410 ± 0.05	7.422 ± 0.03
Arterial blood pCO_2	33.4 ± 6.0	27.1 ± 3.3	33.9 ± 5.0	35.9 ± 8.0	34.3 ± 4.6
Mean arterial BP	111.6 ± 12.6	107.6 ± 15.4	101.7 ± 15.3	106.3 ± 11.1	105.0 ± 9.5
Cardiac index (liter/m^2/min.)	3.8 ± 0.9	3.1 ± 0.9	3.8 ± 1.1	3.8 ± 0.8	3.8 ± 0.6

pneumonitis and consolidation of the lungs. Representative sections are shown in Figures 2 and 3. In Figure 3 should be noted the preponderance of large monocytic cells in thickened alveolar septa many of which are collapsed together. Other areas as illustrated in Figure 3, disclosed both interstitial and intra-alveolar presence of many polymorphonuclear leukocytes.

The course of the patient presented in Figure 4 is that of a 67-year-old woman who was intermittently in profound hypovolemic shock for 6 hours due to a ruptured abdominal aortic aneurysm. At operation the aorta was replaced with a prosthesis. She received a total of 26 pints of blood. A very large retroperitoneal hematoma was present which could not be removed and was not drained. Twelve hours postoperatively when the first measurements were made, it is of note that she had a marked respiratory alkalosis in the face of arterial hypoxemia and pO_2 of 58 mm. Hg. At that time chest x-ray, except for a general ground glass appearance, was almost normal. By the next day a tracheostomy and a ventilator were required because of severe hypoxia. The x-ray became mottled and streaked, progressing on to evidence of atelectasis.

Her cardiac output was elevated, rising subsequently to a remarkably high value. Throughout her course she maintained a hyperdynamic circulatory state even though her caloric energy expenditure was not significantly elevated. Until 3 days before death, her circulation was adequate. At that time, she began to develop a metabolic acidosis. On the twelfth day the patient suddenly died of a coronary infarction despite apparent recovery from pneumonitis.

These two cases are representative of our experience in studying a series of patients who were suffering from trauma, shock, or sepsis in which respiratory complications were present in 58% with a mortality of 34%. These data are to be presented elsewhere.[48]

Experimental Observations

Five groups of animals were studied for comparative purposes: 1) Laparotomy only to serve as a control, 2) dogs in which the cecum was ligated, 3) dogs submitted to hypovolemic shock, 4) dogs in which a suspension of E. coli and bile were injected into the peritoneum, and 5) rats in which a suspension of E. coli was injected into the peritoneum. Except for preparatory operations, all observations were made without pain on conscious animals.

All dogs were treated with penicillin, 1 million units crystalline, and 1 million units procaine daily in divided doses, before, during, and after the experimental procedure. All animals were rejected in which rhinitis was present prior to the experiment. So, too, were those in which wound infection developed at the site of preparatory operative incisions.

Hemodynamic and Blood Gases

I. Control Group Laparotomy Only. Data on hemodynamic and blood gases from these animals are presented in Table 1-A. Little variation in any of the parameters was observed during uneventful recovery.

II. Cecal Ligation. Following a preliminary study, the animals were anesthetized and the cecum ligated after expressing fecal matter from it into the ascending colon. The responses of the survivors in this group are given in Table 1-B. The noteworthy points are a moderate depression of both blood pressure and cardiac output on the first day postoperatively, at the time when the animals were developing peritoneal fluid and edema. It should also be noted that there was a significant depression of arterial pO_2 and pCO_2 to a mean value of 76 mm. Hg and 30 mm. Hg, respectively, on the fourth day. This was accompanied by a rise in the arterial pH to 7.49 on the fifth day. Six of these animals were permitted to recover and were sacri-

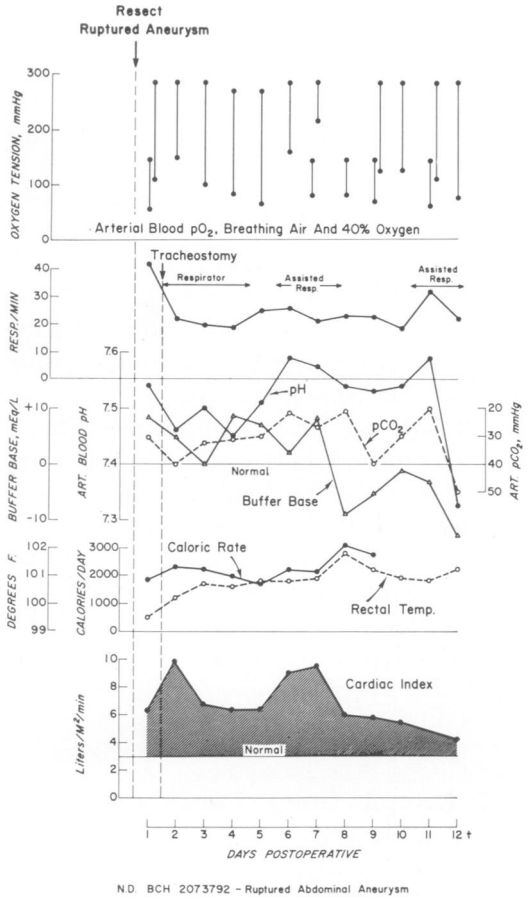

FIG. 4. An example of respiratory insufficiency which developed 1 day after removal of a perforated aortic aneurysm. The patient was in shock for several hours and received 26 transfusions. Note the progressive hypoxemia during first 5 days, refractory to 40% oxygen administration through a tracheostomy. This was accompanied by a severe respiratory alkalosis and a high cardiac output until just before death on the twelfth day. For details, please see text.

ficed on the fourteenth day to obtain pulmonary specimens. In this group, with but one exception, in which multiple abscesses were found, the arterial oxygen tension returned to normal.

III. Hypovolemic Shock. The animals were subjected to a 2-hour period of hypovolemia. A mean arterial blood pressure between 40 and 50 mm. Hg was maintained. Thereafter, blood was reinfused and the animals allowed to recover. The blood gas and circulatory response of this group are presented in Table 1-C. It is noteworthy that little depression of arterial oxygen tension occurred in the postoperative period in this group.

IV. Intraperitoneal Injection of E. coli and Bile. Following the preliminary studies and without anesthesia a phosphate buffer suspension of an overnight broth culture of E. coli containing 10^8 organisms per kilogram of body weight was injected into the peritoneum. Through the same needles, using a second syringe, 10 cc. of sterile dog bile mixed with 100 cc. of normal saline solution was injected. The dogs very frequently became sick, vomited, and defecated. Such deaths as occurred in this series took place in the first 24 hours.

The response of the survivors in this group of animals is presented in Table 1-D. It will be noted that there was a moderate early depression of both arterial blood pressure and the cardiac index. Thereafter, cardiac output tended to rise as did the pressure. The arterial oxygen tension from an average initial value of 90 mm. Hg declined to 85 mm. Hg on the third day. At the time of sacrifice, from the first day onward, these animals were found to have a bloody peritonitis which became purulent by the third day. Coliform bacilli but not other organisms were cultured from the peritoneal fluid in all but four, which were sterile when sacrificed on the third day. No clostridia were present in any. In 34% serosanguinous pleural fluid was found at autopsy.

V. Rats Intraperitoneal Coliform Bacilli. Sprague-Dawley pathogen free rats were employed. These animals were originally bacteria free at birth. Subsequently they were kept under isolated conditions and were entirely healthy as far as could be determined at the time of the experiments. Except for a control group of eight animals, in which there was no mortality, all animals received the same dosage of E. coli suspension as the dogs. The mor-

TABLE 2. *Pulmonary Histology in Dogs with Peritonitis Induced by Cecal Ligation*
Average Value and (Range)

Day of Sac.	No. of Dogs	Body Temp.	Lung Grade	Histology*							
				Alveolar Hemorrhage	Packed Erythroc. in capil. and Interstitial	Alveolar Septal Thickening and Edema	Monocyte Infiltra.	Focal Alveolar Collapse	Focal Atelectasis	Polymorph. Leukocytes	Abscess or Consolidation
Day 1	4	102.0 (101.4–102.6)	I (I–II)	+ (0–++)	++ (+–+++)	+ (+–++)	+ (0–4)	+ (0–++)	0 (0–+)	0 (0–+)	0 (0–0)
Day 2	4	102.6 (102.1–103.6)	II (I–III)	++ (+–+++)	+++ (++–+++)	++ (+–+++)	++ (+–++)	++ (+–+++)	+ (+–+++)	+ (0–++)	0 (0–+)
Day 3	5	103.4 (102.5–103.8)	II (II–III)	++ (++–+++)	+++ (++–++++)	++ (++–+++)	++ (+–+++)	++ (+–+++)	++ (+–+++)	+ (0–++)	+ (+–++)
Day 4	4	103.3 (102.8–104.2)	III (II–IV)	++ (++–++++)	++ (++–+++)	+++ (++–++++)	+++ (+–++++)	+++ (++–++++)	++ (+–+++)	+ (+–+++)	+ (0–++)
Day 5	5	103.0 (102.4–103.8)	III (II–IV)	++ (++–+++)	++ (+–+++)	+++ (++–+++)	+++ (++–+++)	+++ (++–++++)	+++ (+–++++)	+++ (+–++++)	++ (0–++++)
Day 14	6	102.3 (101.8–102.8)	I (I–II)	+ (0–+)	+ (0–++)	+ (+–++)	+ (+–++)	+ (0–++)	0 (0–++)	+ (0–++)	+ (0–+++)

* Graded on scale + to ++++.

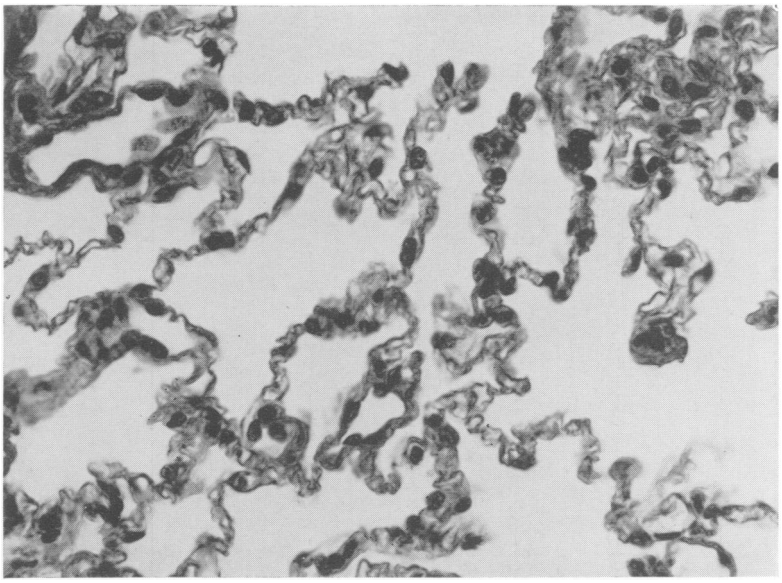

FIG. 5. An example of normal lung from an intact healthy dog, showing thin alveolar septa and the orderly progression of red cells through the capillaries. Original magnification ×250.

tality within the experimental period was 53% but only surviving animals were included. No hemodynamic or blood gas studies were made in this group. They were sacrificed under sterile conditions for bacteriologic examination of the lung and peritoneal fluid. Samples of lung were also obtained for histological examination.

As may be seen from Table 1, the behavior of the dogs with experimental peritonitis was not unlike that of man, as exemplified by the patients whose courses are presented in Figures 1 and 4. In particular, this is true of the group of animals in which cecal ligation was carried out.

Histology

Microscopic examination of the lungs from the dogs with cecal ligation and with intraperitoneal injection of E. coli disclosed a graded progression of lesions. Intracapillary and interstitial congestion of red cells was followed by septal thickening, edema, and an infiltration of monocytic macrophages. Focal alveolar collapse was subsequently accompanied by the presence of polymorphonuclear leukocytes both in the septa and within the alveoli. However, it should be noted that a great variation existed within a given dog's lung ranging all the way from normal to very severe lesions. Often it was difficult to arrive at an average grade. Representative sections of the pathological portions are presented in Figures 6, 7, 8, 9, and 10. Data from the microscopic examination of the lungs in the various groups are presented in Tables 2 through 5.

Normal. For purposes of comparison a section of normal lung is presented in Figure 5. The absence of thickening or edema in the septa should be noted. The erythrocytes are found to be in orderly fashion progressing through the alveolar capillaries. The thin capillary walls appear to bulge into the alveolar lumen. There is no evidence of clot, edema, or leukocytic infiltration in this section. Fat stains of frozen sections from normal lungs disclosed only occasional and minimal accumulations of fat. In no instance were large globules present. Such as existed were found as tiny vacuolated droplets within the macrophages.

Grade I. In Figure 6 is an example in which the alveolar septa are somewhat thickened. There is evidence of infiltration

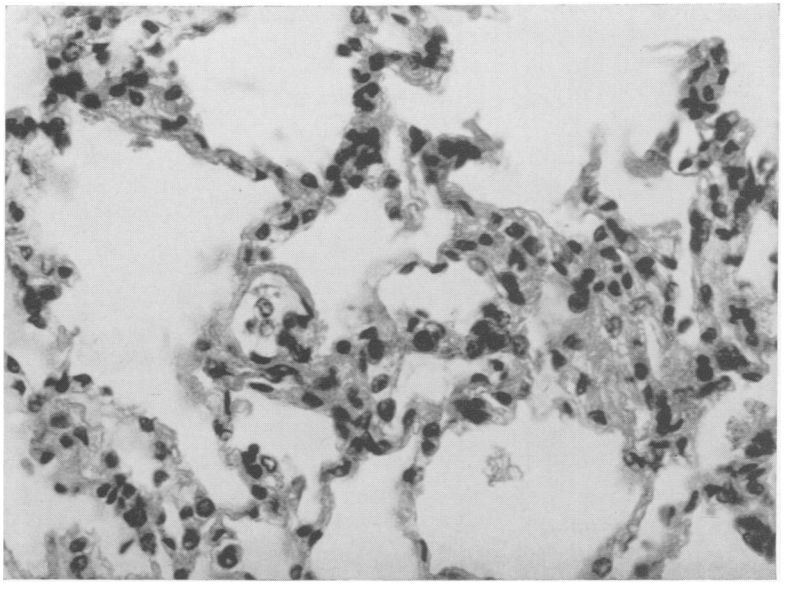

FIG. 6. A representative example of a Grade I lesion from a dog with peritonitis showing thickening of the alveolar septa and some congestion of red cells. Note the presence of monocytes and the comparative rarity of polymorphonuclear leukocytes. Original magnification ×250.

with monocytic leukocytes with dark staining nuclei with light staining cytoplasm. Often they contained vacuoles. Some degree of alveolar collapse gives more of an impression of septal thickening than actually exists. However, this particular aspect of the lesion is minimal. Frequently, there are large quantities of red cells packed into the capillaries and in the interstitial spaces. Occasionally intraalveolar hemorrhage is also present. Fat was found in 84% of the Grade I lung sections. For the most part, it was located as droplets in the large monocytic macrophages.

Grade II. In Figure 7 a more advanced lesion is shown in an animal sacrificed on the second day following the injection of E. coli intraperitoneally. Here the confluence and thickening of alveolar septa has increased with an apparent rounding of the remaining alveolar air spaces. A few polymorphonuclear leukocytes are present. The majority of the leukocytic cells visible are monocytes. There are also interstitial collections of erythrocytes in this section. Fat stains in every instance disclosed large numbers of fat containing macrophages with extracellular fat droplets in the alveolar septa.

Grade III. Lesions are illustrated in Figure 8. Here the alveolar septa contain polymorphonuclear leukocytes and that the thickening of the septa as well as confluence of the focal alveolar collapse has progressed. Often there were large areas of focal atelectasis, especially in the peribronchial regions. Numerous erythrocytes present are in the interstitial spaces and in the intraalveolar spaces. Fat droplets were present in all Grade III lesions both within and outside the macrophages. Often free fat droplets appeared in the alveoli.

Grade IV. The lesion, as illustrated by Figure 9, contains not only numerous polymorphonuclear leukocytes in the alveolar septal interstitial tissue but also in the alveoli themselves. Large areas in Grade IV lesions of confluent pneumonia resemble what is normally considered bronchopneumonia. Areas of atelectasis are common. Even abscesses are found.

As shown in Figure 10, numerous large accumulations of fat in the alveolar septa are observed in the frozen sections of the lungs Graded III and IV. Not infrequently, the globules are broken and appear to be dispersed in the alveoli as well as in the

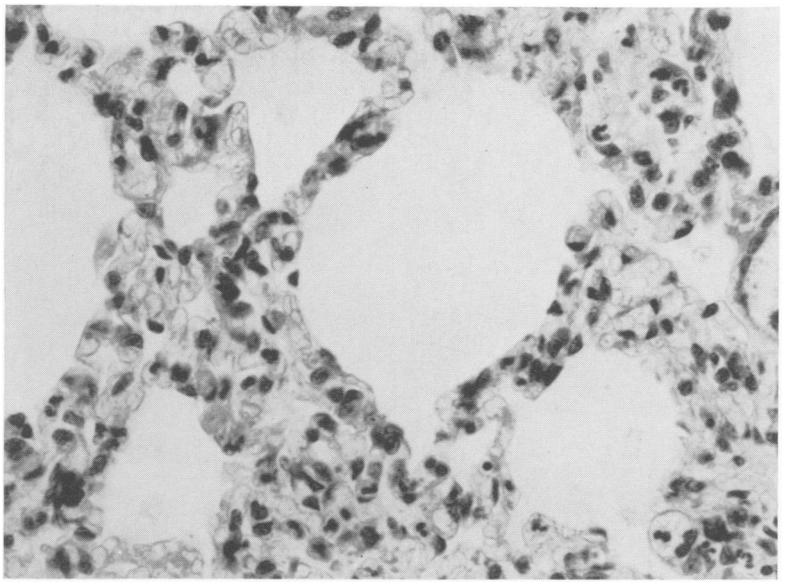

FIG. 7. A representative example of a Grade II pulmonary lesion showing marked thickening of the septa and focal alveolar collapse. Erythrocyte congestion and numerous monocytes are present as are a few polymorphonuclear leukocytes. Original magnification ×250.

walls. The macrophages also contain large numbers of brightly stained fat droplets.

Rats. The histological appearances of the lungs of the pathogen free rats were similar to those observed in the dogs. In the control animals, except for a very slight red cell congestion, the lungs were normal. Using the same method of grading the lesions, the pulmonary responses to intraperitoneal injection of a suspension of E. coli are presented in Table 5. The same progression as in the dogs occurred. Within half an hour after injection a marked packing of red cells occurred in the capillaries and interstitial spaces. There was also hemorrhage into the alveoli. At 8 hours septal thickening and monocytic infiltration were present, accompanied by focal alveolar col-

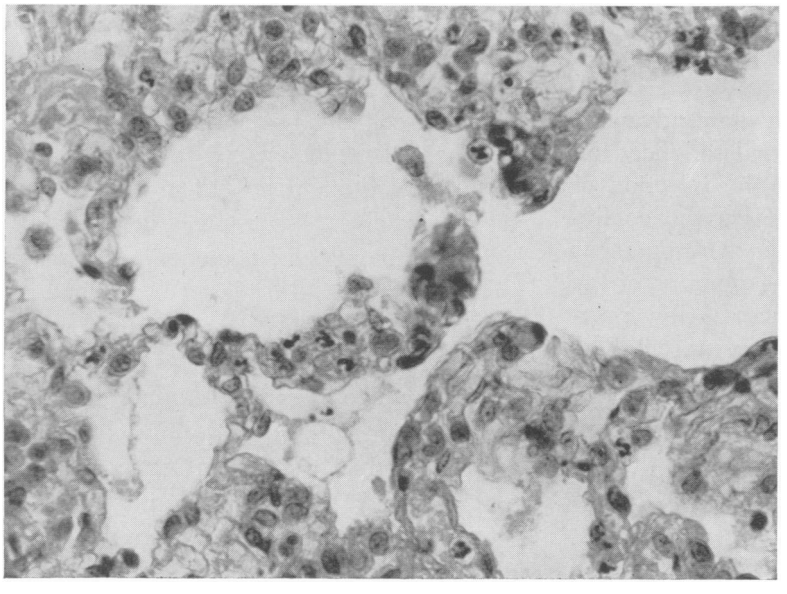

FIG. 8. A representative section of a Grade III pulmonary lesion in a dog with peritonitis showing marked thickening of the septa and alveolar collapse with rounding of the remaining air spaces. Numerous red cells and polymorphonuclear white cells are present. There is interstitial and intraalveolar proteinaceous material present. Original magnification ×250.

lapse. This aspect was more pronounced after 1 day, at which time polymorphonuclear leukocytic infiltration became prominent. In contrast to the dogs, the surviving rats began to clear their lungs within 48 hours, and by 72 hours the majority resembled those in the control group.

Bacteriology

Cultures from the lungs of dogs subjected to cecal ligation were obtained in only eight instances. From the group with hypovolemic shock there were only three. The number is too small to draw conclusions, but it is significant that clostridia were cultured in none. From the dogs and rats given intraperitoneal injections of E. coli, the bacteriological data are presented in Tables 4 and 5. Forty per cent of the dog lungs were sterile, and the presence of E. coli appeared to bear little relationship to the stage of the pulmonary lesion. During the period of most intensive reaction in the rat lungs the presence of a positive culture ranged from 0 to 66%. The almost complete absence of other organisms in the pulmonary cultures from both groups of animals is particularly striking. This suggests that invasion had not occurred even in the dogs with Grade IV lesions.

Gas Exchange

The relationship of the arterial blood gases at the time of sacrifice to the extent of the pulmonary process is presented in Figure 11 for those dogs from which both types of data are available.

The control animals and those with Grade I lesions showed no significant abnormalities. There was a progression downward of arterial oxygen tension accompanying the more advanced lesions. The mean value for the Grade IV lungs was 73 mm. Hg. In all stages the majority of animals exhibited a respiratory alkalosis, manifested by arterial pH values up to 7.52 and carbon dioxide tensions as low as 14 mm. Hg. The ma-

TABLE 3. *Pulmonary Histology in Dogs After Hypovolemic Shock*
Average Values and (Range)

Day or Hour of Sac. after Reinfus.	No. of Dogs	Body Temp. at Sac.	Lung Grade	Histology*							
				Alveolar Hemorrhage	Packed Erythroc. in capil. and Interstitial	Alveolar Septal Thickening and Edema	Monocyte Infiltra.	Focal Alveolar Collapse	Focal Atelectasis	Polymorph. Leukocytes	Abscess or Consolidation
4 hours	3	100.2 (99.2–101.0)	I (I–II)	+++ (++–++++)	+++ (++–++++)	+ (+–++)	+ (+–++)	++ (+–++)	++ (+–++)	+ (+–++)	0 (0–0)
1 Day	3	102.8 (102.2–103.4)	II (I–III)	+++ (+–++++)	+++ (++–++++)	+++ (++–++++)	+++ (+–++++)	+++ (+–++++)	+++ (+–++++)	++ (+–++++)	0 (0–+)
2 Day	2	102.6 (102.0–103.2)	III (I–IV)	++ (+–+++)	++ (+–++++)	++ (+–++++)	+++ (++–++++)	+++ (++–++++)	++ (+–++++)	+++ (++–++++)	+ (+–++)
3 Day	4	102.2 (101.4–103.2)	II (I–III)	++ (+–++)	++ (+–++)	++ (+–++)	++ (+–++)	++ (+–++)	++ (+–++)	++ (+–++)	++ (+–+++)

* Graded on scale + to ++++.

TABLE 4. *Pulmonary Histology and Bacteriology in Dogs With Induced Peritonitis Intraperitoneal Injection E. Coli Plus Bile*

Day of Sacrifice	Dog #	Body Temperature at Sacrifice	Grade	Histology*								Bacteriology	
				Alveolar Hemorrhage	Packed Erythrocytes in Capillaries + interstitial	Alveolar Septal Thickening and Edema	Monocyte Infil.	Focal Alveolar Collapse	Focal Atelec.	Polymorph. Leukocytes	Abscess Consol.	E. Coli	Other Organisms
Normal control	1. 3625	101.6	0	+	+	+	0	0	0	0	0	0	0
	2. 3841	102.2	0	0	0	0	0	0	0	0	0	0	0
	3. 3839	102.0	0	0	0	0	0	0	0	0	0	0	0
	4. 3837	102.0	0	0	+	±	0	0	0	+	0	0	0
Intact dogs with rhinitis	1. 3812	103.2	II	0	+	++	+	+	+	++	+	0	S. Aureus
	2. 3814	103.4	I	0	0	+	+	0	0	+	0	0	S. Aureus
Peritonitis day 1	1. 3788	103.6	II	0	+	+++	++	++	++	+	0	positive	0
	2. 3739	103.2	I	0	+	++	++	++	+	+	0	0	S. Aureus+
	3. 3760	103.4	II	+	+	++	++	++	+	+	0	positive	0
Peritonitis day 2	1. 3714	101.0	I	+	++	+	++	+	0	+	0	0	0
	2. 3715	102.8	II	0	0	++	++	++	+	+	0	positive	0
	3. 3711	103.8	I	0	+	+	+	0	0	+	0	positive	0
	4. 3643	103.0	IV	+	+	+++	+++	++++	+++	++++	+++	positive	0
	5. 3796	101.8	III	+	+++	++	+++	+++	++	++++	++	0	0
	6. 3800	105.0	II	0	+	++	++	++	++	0	0	0	0
Peritonitis day 3	1. 3670	104.2	III	++	++	++	+++	++	++	+	0	positive	0
	2. 3699	103.7	II	0	++	++	++	++	++	0	0	0	0
	3. 3112	103.0	I	+	+	+	++	+	+	0	0	0	0
	4. 3694	102.9	III	+	++	+++	+++	+++	+++	++	+	0	0
	5. 3789	102.0	III	++	++	+++	+++	++	+++	±	0	positive	0
	6. 3684	105.0	II	+++	++++	++	++	+	+	+	0	0	0
	7. 3615	105.0	III	+++	+++	+++	++	+++	++	+++	++	positive	0
	8. 3636	104.0	II	+	+	++	++	++	+	+	0	positive	0
	9. 3637	101.0	II	0	+	++	++	++	+	+	0	positive	0
	10. 3657	103.0	IV	++	+++	++++	++++	+++	+++	+++	+++	positive	0
	11. 3643	102.0	III	++	+++	++++	+++	++	+++	++	0	positive	0

* Graded on scale + to ++++.

jority of the pCO_2 values fell between 28 and 40 mm. Hg.

Discussion

A clinical syndrome of pulmonary dysfunction may follow trauma and shock [13] or may accompany extensive infection elsewhere in the body.[6, 12] As illustrated by the course of the patients presented in Figures 1 and 4, respiratory insufficiency is usually ushered in by a moderate arterial hypoxemia [2] and may be accompanied by respiratory alkylosis.[26] The pattern is characterized by "physiological shunting," defined as the passage of a portion of the blood through the lungs without taking part in gas exchange.[27] The gross mismatching of perfusion and ventilation can be demonstrated by the failure of the arterial oxygen tension to increase normally when oxygen in high concentrations is breathed.

As is shown by the two patients who are typical of those with peritonitis or postshock, the cardiac output is inappropriately high in comparison with the metabolic expenditure of energy. Perhaps it is related to a reduced oxygen uptake in the periphery, as suggested by Siegal *et al.*[41] Our previous experiments and examination of the circulation in patients with peritonitis indicated that large A-V shunts may be present in areas of inflammation.[1, 12] In any event, the flow of blood through the lungs is high under these conditions.

Furthermore, it appears unlikely that atelectasis and pneumonia are caused entirely by failure to breath deeply. If anything, these patients are overbreathing to maintain a respiratory alkylosis. At the same time clinical recognition of the dangers of pulmonary complications leads to emphasis upon continued insistence on coughing and deep breathing. Therefore, one must look further for the cause of the high incidence of pneumonitis among patients suffering from fulminating sepsis in other parts of the body.

The physiological behavior of the dogs with experimentally induced peritonitis suggests that a similar process takes place in these animals in the face of extensive sepsis. The concept is reinforced by the similarity of the histological lesions in the pulmonary alveoli and septa observed in postmortem specimens (Fig. 2, 3) to the Grade III and IV lesions obtained from animals sacrificed on the third to the fifth day after the induction of peritonitis (Tables 2, 4, and 5). Examples of these more advanced lesions are given in Figures 8 through 12.

The data derived from these studies as well as those from others who have studied experimentally the lungs following shock [8, 22, 40] endotoxin shock [17, 28] and after prolonged extracorporeal perfusion [30, 31] suggest that there is a pattern of pulmonary reaction common to these situations as well as to the presence of severe infection. All are characterized by an early interstitial hemorrhagic lesion followed by an inflammatory phase.

Initially, red cells are packed in the alveolar capillaries and into the tissue spaces surrounding them, causing a thickening of the septa (Fig. 7). In its more severe forms some of the alveoli may also be filled with erythrocytes. As is shown in Table 3 the hemorrhagic aspect was prominent very early in the dogs subjected to hypovolemia. However, in the animals with peritonitis sacrificed at or shortly after the period of reduced cardiac output a similar and frequently severe degree of the hemorrhagic lesion was present (Tables 2 and 4).

The thickened edematous alveolar septa appear to be enlarged and increased in numbers. The numerous monocytes with large deeply staining nuclei and pale cytoplasm are probably from the circulation.[34] That they are phagocytes is attested to by the number of vacuoles present. Stains with Oil red O and Sudan B of frozen sections taken from these lungs show the large

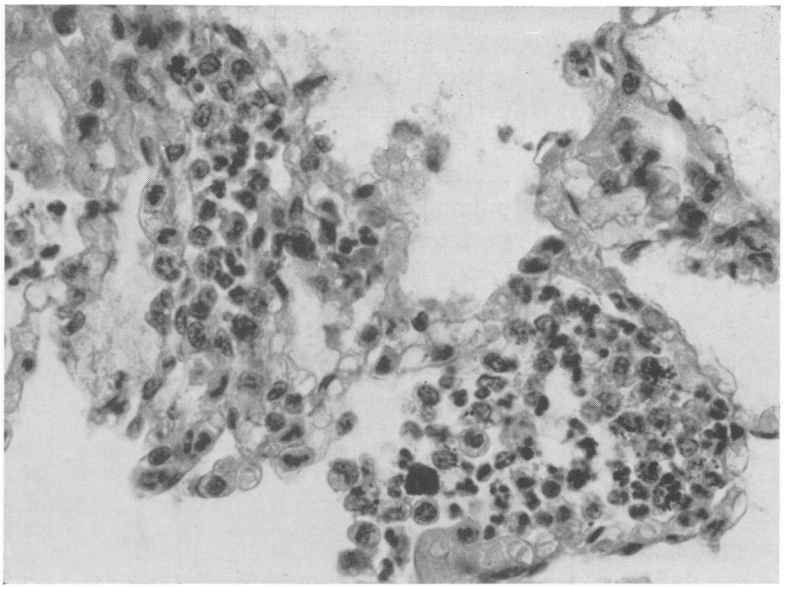

FIG. 9. A representative section of a Grade IV pulmonary lesion from a dog with peritonitis exhibiting numerous polymorphonuclear leukocytes both within the alveoli and in the grossly thickened septa. Original magnification ×250.

monocytic cells to contain quantities of lipid or fatty acids in fine droplets.

Focal alveolar collapse begins to take place, often within a few hours as shown by Tables 2, 3, 4, and 5. In both the animals subjected to hypovolemia and in those with peritonitis, the lesion progresses on to infiltration of the septa with polymorphonuclear leukocytes and intraalveolar collections of white cells. Areas of peribronchial atelectasis or confluent pneumonia are the ultimate consequence, as illustrated in the Grade IV lesions, an example of which is given in Figure 9.

In consideration of the etiology of this sequence of events, hemorrhage followed by inflammatory and alveolar collapse, one is struck by the common pattern under all conditions examined except in the normal controls. Some element of low cardiac output at one stage or another are common to all. Although it appears that the administration of saline reduced the low output state and possibly ameliorated the hemorrhagic state of the lungs in both groups of dogs with peritonitis, the differences were not significant in terms of the lung lesion. Hardaway[21] demonstrated a hypercoagulable state in endotoxic shock and concluded that emboli and thrombosis of small vessels may well be responsible for the events leading to death. Others have confirmed this[17] and has shown intravascular fibrin formation by electronmicroscopy.[28] Whether this phenomenon is entirely responsible for the congestion of red cells is open to doubt. So, too, is the thesis that left heart failure may be responsible. Henry *et al.*[22] failed to find an elevation of the left atrial pressure in animals except transiently after reinfusion of blood. In Gerst's series of experiments on dogs subjected to hypovolemic shock the pulmonary artery pressure fell to a fixed value where it remained.[20] At the same time he measured a marked increase in the ventilation perfusion ratio from which it was concluded that large numbers of alveolar septal capillaries collapsed when the flow decreased and a critical closing pressure was reached. Our group[5] observed in conscious hypovolemic dogs that the difference between the pulmonary arterial and left atrial pressure remained quite constant. During very low flow states a 3 to 5 cm. H_2O difference existed between the "wedge" pressure and

TABLE 5. *Pulmonary Histology in Rats With Induced Peritonitis by the Intraperitoneal Injection of E. Coli + Bile*

Time of Sacrifice after Injection	Number of Animals	Histology								Bacteriology	
		Alveolar Hemorrhage	Packed Erythrocytes in Capillaries and Interstitial Spaces	Alveolar Septal Thickening and Edema	Monocyte Infiltration	Focal Alveolar Collapse	Focal Atelectasis	Polymorph. Leukocytes	Abscess or Consol.	% Positive E. Coli	% Positive Other Organisms
Controls no injec.	8	0	+ (0 to +)	+ (0 to +)	0	0 (0 to +)	0	0	0	0%	0%
0.5 hrs.	3	++ (+ to ++) ++	++ (+ to ++) ++	++ (++ to +++) ++	+ (0 to +++) ++	++ (++ to +++) ++	0	0 to +	0	33%	0%
4 hrs.	3	(+ to ++) +	(+ to +++) +++	(++ to +++) +++	(++ to +++) +++	(+ to ++) ++	0 ++	0 to + +	0	33%	0%
8 hrs.	3	(0 to +) +	(++ to +++) ++	(+ to +++) +++	++ to +++ +++	(+ to +++) +++	0 to +++ ++	(+ to ++) ++	0	66%	0%
24 hrs.	8	(0 to ++) +	(+ to +++) +	(0 to ++++) +	(++ to ++++) ++	(+ to +++) +	(+ to +++) +	(0 to +++) +	0	27%	0%
48 hrs.	3	(0 to ++) 0	(0 to +) 0	(0 to ++) +	(0 to +++) 0	(+ to ++) 0	(0 to +) +	(0 to ++) +	0	0%	0%
72 hrs.	6	(0 to +)	(0 to +)	(0 to +)	(0–4)	(0 to +)	(0 to +)	(0 to +)	0	16%	0%

* Graded on scale + to ++++.

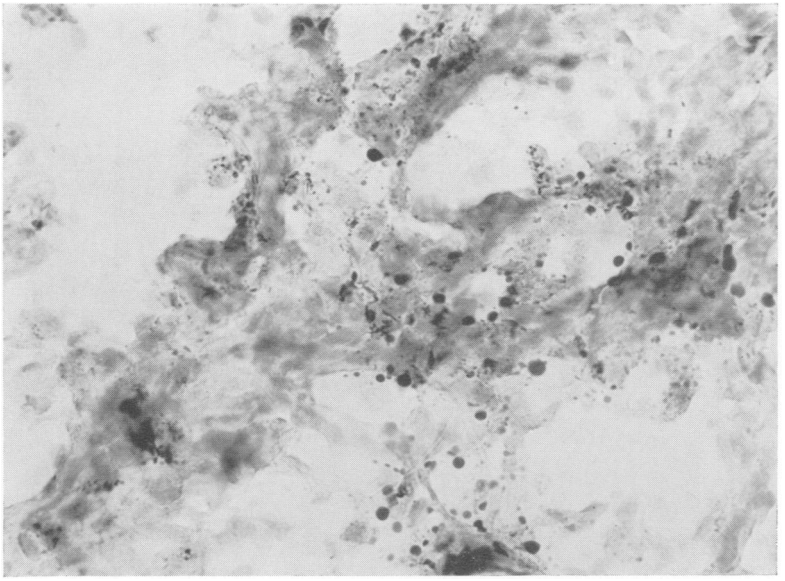

FIG. 10. A fat stain (oil red O) of a frozen section of a lung from a dog with peritonitis which is representative of those with Grade III or Grade IV lesions. Note the fatty material (dark areas) both inside and outside the macrophages. Original magnification ×250.

that in the left atrium.[5] A similar picture has been observed in certain of the septic animals of this series.[48] Pulmonary venous constriction under these conditions apparently does not produce pressures sufficiently high to cause congestion of the capillaries during the period of shock.

All of these morphologic changes, both red cell congestion and the infiltration of luekocytes, occur during the shock period or are present immediately afterward as shown in Table 3. Willwerth[46] isolated one lung by a tourniquet around the hilum during hypovolemia. Although the lung appeared normal after the experiment, more than half of the isolated lungs showed characteristic alterations in dogs sacrificed 24–72 hours later. A similar situation was observed in lungs isolated during prolonged extracorporeal circulation by Nahas *et al.*[30]

Therefore, the conclusion cannot be escaped that the presence of circulating agents such as endotoxin or products of tissue necrosis may be responsible for action on the alveolar capillary[9] and red cell membranes leading to their agglutination[24] as well as to their diapedesis into the interstitial septal spaces.

A similar observation was made by De Palma *et al.*[17] in rats subjected to endotoxemia. Rupture of capillaries, fibrin deposit, and clumping of leukocytes within the capillaries were found by electronmicroscopy in the lungs of these animals.

The subsequent inflammatory aspects of the lesion characterized by monocytic phagocytes may possibly be set in motion by the extravascular presence of blood elements and bacteria. It is true that the process frequently occurred in lungs at all stages of peritonitis in which no organisms could be cultured from the lungs (Tables 4 and 5). Yet this does not prove that organisms may not have been present previously. It is difficult to explain the advent of polymorphonuclear leukocytes in the absence of cultivatable coliform bacteria or other secondary invaders. Yet this was a not infrequent experience.

The most common finding was the presence of fat both within and without the macrophages in all stages of the developing pneumonitis in those experiments. Scully[39] found fat droplets in the lungs in 90% of the autopsies performed upon soldiers wounded during the Korean War. On

the other hand, evidence of true fat embolism was present in only 19% of this group. Free fatty acids injected into the circulation establish an inflammatory response in the lung which is almost identical to that found in these experiments.[14, 23, 33, 38] The clinical response of patients with fat embolism as presented by Sproule[42] is not unlike that of patients shown in Figures 1 and 4. It has been shown that if fatty embolism is survived a pneumonitis develops several days later. This may be related to release of free fatty acids by lipases within the lung itself. One can only speculate on the role of fatty acids possibly released by deteriorating tissues or bacteria in other parts of the body or as a result of lipoprotein denaturation.[15] Waddel[45] suggested that fatty acids may be released during the mobilization of fats by circulating catecholamines. Fatty degeneration of leukocytes and other cells within the lung itself could be the source of the large amounts of stained fat in these sections. Whatever the source, it is evident that conjugated fats are present in these lungs. Lipases may then be responsible for release of the toxic long chain fatty acids[30] into the local tissues.

Bearing these matters in mind it is little wonder that alveolar collapse occurs. Henry *et al.*[22] demonstrated a reduction of surfactant following shock, at the same time finding a reduction in the incorporation of radioactive phosphate into the phospholipids of the lung. This they attributed to a failure of surfactant production by the pneumatocytes. Others have observed a reduction of surfactant activity in the presence of blood[44] or pulmonary transudates.[36, 37] Cooper *et al.*[15] also found a reduction of surfactant following burns which was believed related to the entry of plasma into the alveoli. Oren *et al.*[32] have shown that by contrast to other macrophages the "alveolar macrophages" have a relatively high metabolic rate and are dependent on aerobic processes for energy production. This leads to the conclusion that perfusion insufficiency and edema may lead to failure of surfactant production and other functions. The resultant ischemic hypoxia of the lung may be an initiator of a defective metabolic sequence.[10, 22, 47]

From a therapeutic standpoint, one can only speculate on the possibility that the use of corticosteroids under these conditions may block the inflammatory response by their effects on membranes. Ashbaugh[3] has produced evidence of improved gas exchange in patients with fat embolism.

Another matter of concern is the possible relationship of the low cardiac output in the early stages of developing sepsis as a contributor to the onset of the pulmonary reaction. Although this aspect of the phenomenon is less easy to demonstrate, it is suggested that avoidance of the low output syndrome by the intravenous administration of adequate volumes of saline, Ringer's solution, colloids, or blood when indicated, may well reduce the production of agents responsible for the initial red cell congestion.

The use of respirators with an endotracheal tube or a tracheostomy becomes obvious as respiration fails. But if a volume controlled machine is employed allowing an adequate expiratory phase of at least 60% of the cycle, excellent results are at times attainable as in the response of the patient shown in Figure 4.[11]

Summary

1) Patients suffering from extensive fulminating infection are prone to develop a pneumonitis which may lead to atelectasis, confluent pneumonia, and abscesses. Histologically this is characterized by edema and congestion of the alveolar septa with red cells, monocytic leukocytes, and polymorphonuclear leukocytes. The condition is recognized initially by the presence of moderate hypoxemia and respiratory alka-

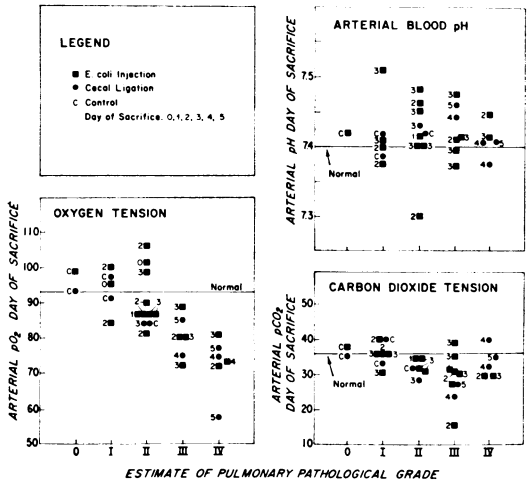

FIG. 11. The relationship of the arterial blood gases and hydrogen ion concentration at the time of sacrifice to the estimated stage of the pneumonitis. Note the hypoxemia in the animals with the more severe lesions, whereas, some degree of respiratory alkalosis was present in the majority of animals with peritonitis at all stages.

losis. As the process progresses, severe respiratory failure follows in a large proportion of the patients. Two clinical examples are presented.

2) To study the pathogenesis of this lesion, physiological and histological observations were made in control animals subjected to laparotomy and in three experimental series. The response to peritonitis induced by cecal ligation was similar to that found in the patients. An initial period of low cardiac output and hypotension was followed by an elevation of both circulatory flow and pressure. For comparative purposes animals subjected to hypovolemic shock and another group with peritonitis caused by the intraperitoneal injection of E. coli and bile were examined. A reduction of arterial oxygen tension and a respiratory alkalosis occurred in the dogs with cecal ligations.

3) Except for the control animals all others exhibited an early intracapillary and interstitial congestion of red cells. Subsequently, septal thickening, edema, and an infiltration of monocytic macrophages was observed. Focal alveolar collapse was common at this stage. Numerous polymorphonuclear leukocytes both in the septa and within the alveoli appeared later. All except the controls contained large amounts of fat in the lungs. Pathogen free rats after injection of E. coli into the peritoneum exhibited the same reaction. Bacteriological culture of the lungs at all stages revealed a high proportion to be sterile. The remainder preponderantly grew out E. coli.

4) The probability is discussed of the various progressive stages representing a common inflammatory reaction to circulating bacteria, endotoxin, or products of degenerating tissues. The possibility that free fatty acids may be important causative agents in this process is suggested.

5) Therapeutic and preventive measures including adequate intravenous fluids, corticoids, and the use of respirators are considered.

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Discussion

Dr. Watts R. Webb (Dallas): I think these studies further establish that the lung is one of the most vulnerable end organs in protracted shock, or, in fact, even in acute stages of low flow states. Dr. Sugg, working in our laboratory with hemorrhagic shock, and Dr. Baxter and Dr. Cook, working with burn shock, have shown changes somewhat different from those Dr. Clowes has shown you in his microscopic slides. The acute changes consist of congestive atelectasis, with collapse of the lung, red cell infiltration, early leukocytic infiltration, and alveolar filling with red cells.

This is not a bacteremic phenomenon, in the acute stages at least, because this picture can be produced in the completely sterile situation after 2 hours of hemorrhagic shock at a pressure of 40 mm. Hg, which is not a very severe shock preparation. The question of whether or not this is heart failure, we believe, has been ruled out, because the heart is very resistant to shock, and fails only in the very late stages. Hemodynamic studies reveal that left atrial pressures throughout this period are always low, rather than high.

Catheterization of the pulmonary circulation from both sides (that is, both the venous and the arterial) confirms the work of Dr. Al Hyman, of New Orleans, and Dr. Oscar Creech, to demonstrate that there is no constriction of the pulmonary arteries or arterioles, or even the arterial wedge position. Instead, there is a constriction of the pulmonary small veins—not the large veins, but the small veins, and not of the pulmonary capillary bed.

In addition, it is not a sludging phenomenon, because ordinarily, in the normal lung, there is an active recruitment of only a very small proportion of the pulmonary capillary bed. However, in this phenomenon virtually all of the capillary bed is very widely dilated, as can be demonstrated by dye or microscopic studies. In attempts at prophylaxis of this, we have not found that atropine or acetylcholine or cortisone or the antihistaminics or vagotomy or hilar stripping have been of any value in protecting the lung against the development of congestive atelectasis in shock.

The only way we have been able to prevent this is by resecting the lung and reimplanting it; the reimplanted lung does not develop the picture of congestive atelectasis, as does the contralateral lung. This suggests to us that this is a neurally mediated phenomenon, and not mediated (at least acutely) by the vascular end products of end metabolism.

Again, I congratulate Dr. Clowes on a very excellent study. These studies will be of great help in the further treatment of our patients.

Dr. George H. A. Clowes, Jr. (Closing): I would like to thank Dr. Webb for his discussion of the shock aspects of this subject. While I was discussing sepsis, time did not permit the discussion of the details concerning the slide which I presented on the shock picture. It shows exactly the difference that Dr. Webb mentioned between wedge pressure and left atrial pressure. We think this may have something to do with the phenomenon of red cell accumulation.

At present I can not say whether red cell congestion of the septa is due to shut-off of vessels and skimming; whether it is due to ischemia of parts of the lung in the low flow state, or to the formation of clots and thrombi, as has been suggested by Colonel Hardaway. Further, it is possible that this "red cell packing" is related to changes in membrane charges on the surface of cells and vessels. If so, this could represent the effect of a circulating agent released by deteriorating tissue or killed bacteria.

The fact remains that we see this red cell packing and hemorrhage in the septic states as well as in shock. The one thing that has come out of this study, in my mind, is that we are looking at a common phenomenon. It is the lung's reaction to this kind of stress that is common to shock, to sepsis, and to trauma.