# Circulating Factors in the Etiology of Pulmonary Insufficiency and Right Heart Failure Accompanying Severe Sepsis (Peritonitis)

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Circulatory failure [6, 9, 19] and respiratory insufficiency [8, 11] have been recognized as the principal terminal causes of death from acute fulminating infection anywhere in the body. The pulmonary lesions associated with peritonitis and other nonthoracic fulminating infections which progress on to atelectasis and bronchopneumonia [28] have been demonstrated experimentally.[10, 11] Evidence shows that the same process may occur also in man.[11, 26] In the early stages interstitial edema containing fibrin is accompanied by invasion of mononuclear leukocytes and margination of leukocytes in the vasculature of the lung.[10, 35] Congestion of the vessels with red cells and the presence of microthrombi are common. Although radiographs of the lung initially show little change, local diffuse alveolar collapse appears to occur early. Admixture of unoxygenated venous blood in the pulmonary veins is evidence of a reduction of the ventilation–perfusion ratio.[29] These changes may be responsible for an elevation of the pulmonary vascular resistance as well as hypoxemia.

Characteristically in the presence of severe sepsis the peripheral vascular resistance is low. The cardiac output must be maintained at a high level to satisfy not only the metabolic requirements of the uninvolved tissues but also the inefficient circulatory run off which occurs in the arteriovenous shunts located in the inflammatory region and elsewhere.[9, 14] The presence of hypoxemia contributes further to the circulatory demand. Inability of the cardiovascular system to maintain the continued high cardiac output results in peripheral vascular constriction in the tissues still able to respond and is accompanied by a progressive metabolic acidosis.

Clinical observations presented in this report suggest that the circulatory insufficiency encountered terminally in these patients may be the result of the pulmonary lesions. The lung changes appear to be responsible to some extent for right heart failure as well as a reduction of oxygen transmission. Results of two experiments examine more closely the development of hemodynamic and morphologic responses of the lung to acute sepsis in the form of peritonitis induced by a standardized method. Serial hemodynamic and metabolic

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TABLE 1. *Causes of General Peritonitis in Patients Studied*

| | Survivors | Deaths |
|---|---|---|
| Average Age Range | 48 (11 to 66) | 57 (29 to 74) |
| Pancreatitis | 2 | 1 |
| Contamination | 2 | 2 |
| Disrupted intestinal suture line | 2 | 2 |
| Perforated duodenal ulcer | 3 | 1 |
| Ruptured gallbladder | 1 | 1 |
| Gangrene small intestine | 3 | 2 |
| Trauma of small intestine | 1 | |
| Perforated appendix | 3 | 1 |
| Perforated colon | 3 | 4 |
| Strangulated ovarian tumor | 1 | 1 |
| Septic abortion with peritonitis | 1 | 1 |
| Total | 22 | 16 |

observations were made on conscious animals after peritonitis was induced by cecal ligation and intraperitoneal instillation of colonic bacteria. Through previously placed conduits, needles could be inserted painlessly into the left atrium and pulmonary artery to determine hemodynamic changes in the lung itself as the disease progressed.

The technic employed for the second series of experiments involved extracorporeal perfusion of the isolated vasculature of healthy dog lung *in situ*. When blood from a healthy animal is perfused through the test lobe neither hemodynamic nor morphologic changes occurred.[13] By incorporating into this perfusion system an intact dog with acute peritonitis induced by the same method, it was proved possible to determine the alterations in perfusion pressure of the test lobe. Progressive histologic changes were observed on serial biopsies of the perfused lung.

These data lead to suggestions concerning the prevention and treatment of these often fatal combined pulmonary and circulatory disorders.

## Clinical Observations

**Methods and Materials.** Patients suffering from generalized fulminating peritonitis were selected for study from the wards of the Fifth (Harvard) Surgical Service of the Boston City Hospital and the Medical College Hospital of Charleston, South Carolina. Adequate hemodynamic, metabolic and blood gas data for comparative purposes were obtained from 38 of these patients. Twenty-two of them survived and 16 died. The ages and causes for peritonitis are presented in Table 1. Although the average age of those who died is 57 compared to 48 for the survivors, the two series are comparable in terms of etiology.

Cultures were obtained from all patients. The flora was mixed, but in all instances contained coliform and other gram-negative enteric organisms. Blood cultures were positive at one time or another in 14% of the survivors and 26% of the deaths. Appropriate antibiotic agents were administered. Rehydration in the early stages of the illness was accomplished with normal saline and Ringer's lactate solution. More recently plasma has been employed. Respirators with endotracheal or tracheostomy tubes were employed when severe hypoxemia or circulatory deficiency existed. The surgical treatment was not unusual. All patients with but one exception, a septic abortion, were operated upon at some stage of the disease. Peritonitis involving a perforated viscus was treated by drainage, exteriorization, or diverting procedures. Others underwent resection to stop continued contamination. Serial metabolic and hemodynamic measurements were made daily or more often as indicated. Arterial blood pressure (BP) and central venous pressure (CVP) were recorded by strain gauges through catheters lying in the radial artery and antecubital vein, respectively. The tip of the venous catheter was positioned in the superior vena cava or right atrium. In 10 patients it was possible to insert the catheter, from time to time, into the right ventricle or pulmonary artery to measure the systolic arterial pressure of the pulmonary circuit. Blood withdrawn from the ar-

terial cannula was analyzed for gases, pH, and hematocrit. The cardiac output was measured by the dye dilution technic, employing indocyanine green. Details of these methods are recorded elsewhere.[9, 11]

**Results.** Representative of the data obtained are the clinical courses of two patients presented in Figures 1 and 2.

**Case 1.** A 41-year-old woman entered the hospital complaining of rectal bleeding and difficult defacation of 9 month's duration. In addition to squamous cell carcinoma of the anus, a diagnosis of carcinoma of the uterine cervix was also made. After preoperative irradiation, 2,000 rads, the patient underwent a combined hysterectomy and Miles resection with removal of the posterior vaginal wall which was invaded. Postoperatively she had a brief period of hypotension, probably about one hour, with a BP of 65/40. The CVP was −3 cm. $H_2O$ which was corrected by blood transfusions. An arterial blood sample disclosed a moderate acidosis of 7.28 and an arterial $P_{O_2}$ of 86 mm. Hg while breathing room air.

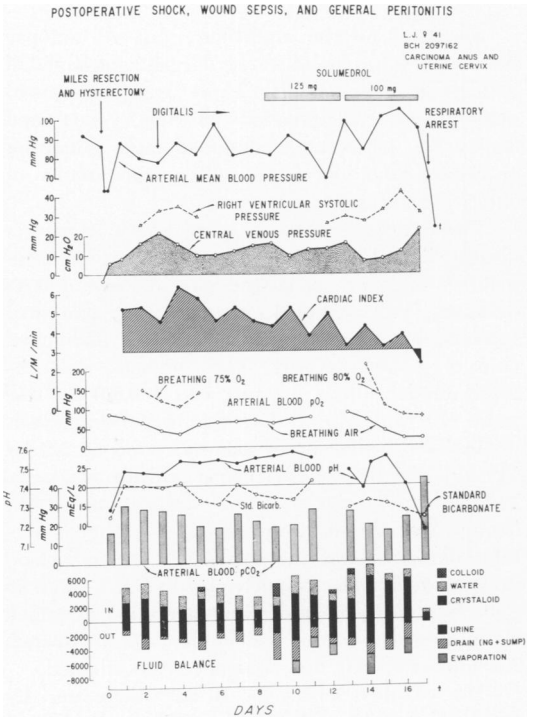


FIG. 1. The clinical course of a severely septic patient who died with pelvic infection and peritonitis. Note the elevation of central venous pressure and right ventricular systolic pressure at the times of severe hypoxemia. Please see the text for details.

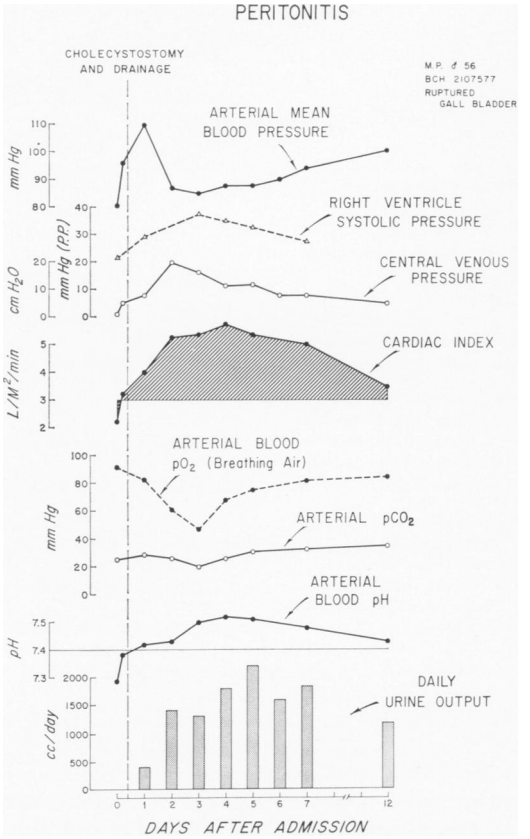


FIG. 2. The clinical course of a patient who recovered from infected bile peritonitis secondary to a ruptured gangrenous gallbladder. Attention is drawn to the elevation of the central venous pressure and right ventricular systolic pressure on the third day when hypoxemia was maximal. At this time respiratory alkalosis was present, a feature which is characteristic of these patients. For details please see the text.

She appeared to do well after this episode, but the following day her cardiac index was 5.3 L/M²/min. She became febrile during the next 2 days, and drainage appeared from the lower pole of the laparotomy incision. Crepitus appeared and pus was drained on the third day which cultured coliform organisms and hemolytic *Staphylococcus aureus*. The central venous pressure rose to 22 cm. $H_2O$ and the right ventricular systolic pressure (RVSP) had risen to 33 from its previous value of 25 mm. Hg. Because of tachycardia to 150 beats per minute, a full digitalizing dose of digoxin was given. This was followed by an increase of the cardiac index to 6.4 L and a further elevation of the RVSP to 35 mm. Hg. At this time, on the

TABLE 2. *Hemodynamic and Metabolic Values in 38 Patients with Generalized Peritonitis*
Average ± Std. Dev. (No. of patients for each measurement)

| | Survivors—22 Patients | | | Deaths—16 Patients | | |
|---|---|---|---|---|---|---|
| | Onset (Day 1) | Maximal Response | Convalescence | Onset (Day 1) | Maximal Response | Premortem |
| Hemodynamic | | | | | | |
| Cardiac index (L/M²/min.) | 3.1±2.1(10) | 4.9±1.4(22) | 4.1±.9(10) | 3.3±1.8(8) | 4.7±1.4(16) | 2.2±1.0(9) |
| Central venous pressure (cm. $H_2O$) | 4±3(14) | 9±4(22) | 5±2(14) | 4±4(9) | 12±5(16) | 19±5(9) |
| Pul. art. or rt. vent. syst. pres. (mm. Hg)* | — | 39(30–46)(5) | 29(26–35)(3) | — | 43(36–48)(5) | 40(28–60)(4) |
| Arterial blood pressure (mm. Hg) | 74±11(14) | 91±12(22) | 93±9(22) | 76±11(11) | 90±19(16) | 65±27(14) |
| Arterial blood gasses | | | | | | |
| Oxygen tension (breathing air (mm. Hg) | 82±10(10) | 62±12(18) | 75±8(12) | 79±14(8) | 53±14(16) | 45±6(10) |
| Carbon dioxide tension (mm. Hg.) | 32±6(10) | 29±6(18) | 34±4(14) | 29±4(8) | 26±9(16) | 42±9(10) |
| Metabolic | | | | | | |
| Arterial blood pH | 7.39±.06(10) | 7.48±.05(18) | 7.44±.03(14) | 7.42±.08(8) | 7.44±.10(16) | 7.21±.08(10) |
| Buffer base excess or deficit (mEq./l.) | −3.±2(10) | −2±3(18) | 0±4(14) | −2±4(8) | −7±4(16) | −12±4(10) |
| Body temperature (°F per rectum) | 100.4±1.5(16) | 101.8±1.9(22) | 100.1±1.1(22) | 101.2±1.7(12) | 102.2±1.4(16) | 99.2±2.1(12) |

* Ranges given in place of standard deviation.

fourth day, the arterial blood $P_{O_2}$ had declined to 35 mm. Hg while breathing air and 115 mm. Hg when 75% $O_2$ was administered by mask. An uncompensated respiratory alkalosis was present with an arterial pH of 7.53. The lung fields were mottled but showed no areas of consolidation or atelectasis. Thereafter she improved although remained febrile to 102.6° F. The posterior wound was opened on the seventh day and irrigations were started. Two days later Klebsiella was cultured from the blood and Gentimycin was substituted for kanamycin therapy.

Because of hypotension, Solumedrol 125 mg.q 8 h was started on the ninth day with improvement of both cardiac output and blood pressure. The arterial $P_{O_2}$ increased on air 60 to 75 mm. Hg during the next 2 days. From the thirteenth day, after the wounds were further explored for undrained pus, she started a progressive downhill course. *Bacillus pyocyaneus* appeared in blood cultures. The ventricular systolic pressure rose to 43 from 27 mm. Hg despite a cardiac index which had fallen to 3.8 L/M²/min. The central venous pressure increased to 24 cm. $H_2O$ terminally. During this period the arterial $P_{O_2}$ declined on room air from 85 to 30 mm. Hg. An endotracheal respiratory tube was necessary during the last 3 days. On the last day she became severely acidotic again (arterial pH 7.16) after ventilation was insufficient, allowing the arterial $P_{CO_2}$ to rise to 43 mm. Hg.

She died on the eighteenth day. At autopsy the lungs were found to be largely consolidated with bronchopneumonia. There was widespread phlegmonous inflammation in the pelvis and flanks. The peritoneum contained large quantities of cloudy fluid and fibrin with mixed culture of enteric organisms.

**Case 2.** A 56-year-old man, whose course is illustrated in Figure 2, entered the hospital complaining of severe epigastric pain of several days duration. Twenty hours previously the pain had subsided but returned with generalized abdominal pain of greater severity. The abdomen was diffusely tender. Blood pressure was 100/60 and the pulse rate was 145. A diagnosis of peritonitis was made. The cardiac index was measured as 2.2 L/M²/min. and the central venous pressure was zero. The hematocrit was 47% and dropped to 43 following the administration of 3.5 L Ringer's lactate solution. After the cardiac index and blood pressure had risen, respectively, to 3.2 L and 96 mm. Hg mean, he underwent operation at which a ruptured gangrenous gallbladder was discovered. A cholecystostomy and drainage were effected.

He remained febrile for 10 days thereafter. By the third day the arterial blood $P_{O_2}$ had dropped to 47 mm. Hg but was accompanied by a blood $P_{CO_2}$ of 20 mm. Hg and an arterial pH of 7.50. The cardiac index rose to 5.3 L/M²/min. associated with an elevation of the right ventricular systolic pressure to 38 mm. Hg. The CVP had risen the

previous day to 20 cm. $H_2O$. Both subsequently declined to normal as the arterial $P_{O_2}$ gradually returned to 84 mm. Hg. The improvement occurred despite the fact that the cardiac index was maintained at greater than 5 L/M²/min. for several more days. Further changes toward normal were accompanied by marked diuresis with urinary outputs ranging from 1,700 to 2,400 ml. per day. Convalescence thereafter was uneventful.

In Table 2 are summarized the pertinent data for comparative purposes between the 22 survivors and the 16 deaths. There are virtually no differences between the two groups during the initial period at the onset of peritonitis. The same is true during the height of the disease when a maximal response might be expected. There were two possible exceptions. The average of the central venous pressure and right ventricular systolic pressure were elevated in both, being slightly higher in the group which ultimately died. However, this difference is not significant. The arterial $P_{O_2}$ declined significantly ($p < 0.01$) in both groups, while breathing air, to 62 and 53 mm. Hg during the period of maximal response, yet the difference between them is again not significant. However, at this time those who were to die showed a greater degree of metabolic acidosis: Buffer Base deficit $-2$ and $-7$ mEq./l. ($p < 0.05$).

The subsequent course of the survivors showed a return toward normal. By contrast the last premortem values which were obtained at times ranging up to 32 hours before death indicated progressive deterioration of both the circulation and the respiration. As cardiac output declined to 2.2 L/M²/min., there was a fall of systemic blood pressure accompanied by continued elevation of the average right ventricular systolic pressure to 40 mm. Hg and a further rise of the central venous pressure to an average of 19 cm. $H_2O$. This reduced circulation was accompanied by progressive uncompensated acidosis (average pH 7.21) as the arterial $P_{CO_2}$ rose to 42 mm. Hg. At the same time a further decline of the arterial $P_{O_2}$ to 45 mm. Hg was observed with no respiratory assistance. In most instances this severe hypoxemia necessitated the administration of oxygen by nasal catheter or respirator.

## Experimental Observations

### I. The Effects of Peritonitis in Intact Conscious Animals

**Methods and Materials.** In order to assess hemodynamic alterations in the pulmonary circuit caused by experimentally induced peritonitis, a preparation was devised which permits measurement of pressures in the pulmonary artery and left atrium without discomfort in conscious dogs. Three or four weeks prior to the time of the experiment conduits constructed of tygon tubing surrounded by a closely fitting knitted dacron arterial prosthesis were implanted by sutures to the inner surface of the thoracic skin and the adventitia of the pulmonary artery. A similar conduit was placed between the skin and the epicardium of the left atrium. After solidly healing into place, these channels permitted a #18 spinal needle to be inserted through a novacaine wheal in the skin directly into the left atrium or pulmonary artery. Two days before the start of the experiment inlying silicone rubber catheters were placed through the femoral vessels under light pentobarbital anesthesia into the right atrium and the aorta. Being fitted with stopcocks, these were kept filled with heparin saline solution and were covered with a circular bandage when not in use. The dogs were trained to lie quietly while measurements were being made. Cardiac output was determined by indocyanine dye dilution curves, and pressures were recorded by strain gauges on an oscillograph.

Only dogs which made an uneventful recovery and gave no evidence of infection, pneumonia, or rhinitis were employed. While fully conscious, several preliminary control hemodynamic studies were carried out. Arterial blood samples were obtained

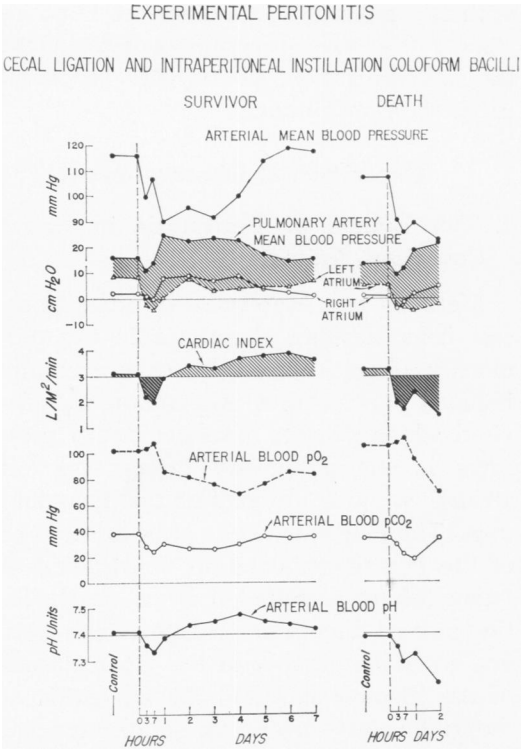


FIG. 3. Representative examples of survivors and deaths among dogs in which peritonitis was induced. Note the reduction of left atrial pressure from the first day onward when the pulmonary artery pressure was elevated.

for gas analysis. Under pentobarbital anesthesia peritonitis was induced by ligation of the base of the cecal appendix. A suspension of a culture of *E. coli* ($10^8$ organisms/Kg. of body weight) was introduced prior to closure of the laparotomy incision. Each dog was treated with penicillin, 1,000,000 units procaine and 1,000,000 units crystaline, daily in divided doses to inhibit the growth of clostridia.

Hemodynamic and blood gas measurements were repeated at four and seven hours, and at daily intervals thereafter until the dog died or was sacrificed. The animals were allowed to drink water ad lib. It later appeared that survival was closely correlated with whether the animals chose to drink postoperatively.

**Results.** Five dogs died within 2 to 4 days after induction of peritonitis. Ten survived. Representative examples from both groups are given in Figure 3. During the first day an initial depression of pressures in the systemic and the pulmonary artery accompanied by a 29 ± 12% reduction of cardiac output was observed in the entire series of survivors. An average 14% rise of hematocrit suggests that this may represent a state of hypovolemia due to fluid translocation. One day later the cardiac output returned to an average 4 ± 8% above the control value. It progressively rose to the fourth day when the average was 26 ± 12% above the preoperative control value. However, the pulmonary artery pressure was elevated by 34 ± 10% on the first day and remained elevated until the fourth day while the left atrial pressure remained lower than normal. At the same time the right atrial pressure was increased by an average of 6 ± 4 cm. $H_2O$ above the control resting level. Thus the transpulmonary pressure gradient from PA to LA was in-

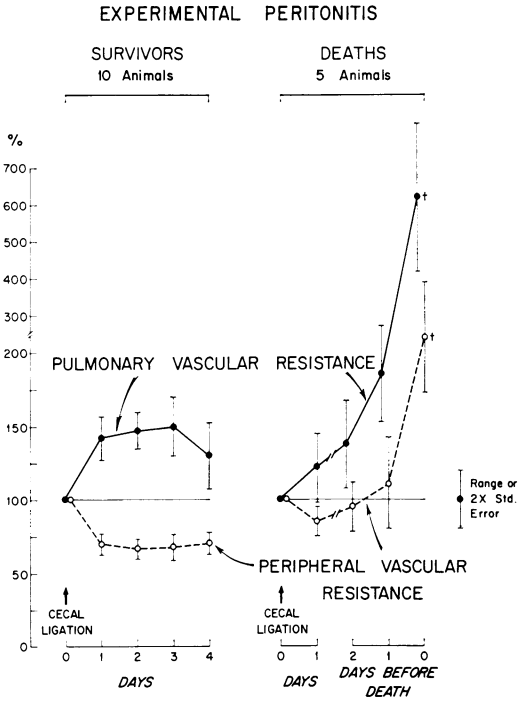


FIG. 4. The average pulmonary and total peripheral vascular resistance changes in experimental peritonitis. The average values are expressed in terms of per cent changes from control values obtained before the peritonitis was induced.

creased by an average of 105 ± 26% on the second and 154 ± 36% on the fourth day (determined by the ratio of PA-LA/CI). The increase of pulmonary vascular resistance which is shown in Figure 4 is in marked contrast to the reduced peripheral vascular resistance. Concomitantly the arterial $P_{O_2}$ declined from an average control value of 98 ± 12 (std. dev.) to 76 ± 10 mm. Hg by the third day. This was accompanied by a decrease of the arterial $P_{CO_2}$ to 28 ± 6 mm. Hg which produced an uncompensated respiratory alkalosis and an arterial pH of 7.46 ± 0.4.

The animals which died behaved in a similar fashion. In some the cardiac output was restored to near normal, but prior to death all exhibited a marked decline. However, the transpulmonary pressure gradient remained elevated and is indicated by the very high pulmonary vascular resistances found in these animals in the last measurements prior to death as shown in Figure 4. The last arterial gas values in these five animals averaged $P_{O_2}$ 68 with a range of 56–76 mm. Hg and $P_{CO_2}$ 36 (range 28 to 46) mm. Hg.

## II. Perfusion of Lung Tissue *in situ*

**Materials and Methods.** Healthy mongrel dogs weighing from 15 to 25 Kg. were used in this study. To carry out extracorporeal perfusion of the test lobe under as nearly normal conditions as possible, the vascular bed of the left lower lobe was isolated and perfused *in situ*. The normal bronchial vasculature, nerve supply and lymphatic drainage were preserved. The preparation is illustrated in Figure 5. The operative procedure has been described in detail in a previous publication.[13]

The circuit was initially primed with 200 ml. of blood, allowed to drain from the left atrium of Dog 1 into the venous reservoir before the cannula was advanced into the left inferior pulmonary vein. Perfusion was effected by a calibrated roller pump which had been previously determined to give a reproducible output. The collapsible plastic reservoir employed was kept free of air, avoiding the presence of an air-blood interface within the circuit. New, saline-washed Tygon tubing (¼″ I.D.) was used for each experiment and discarded after use. All glass connections were carefully siliconized and washed prior to use.

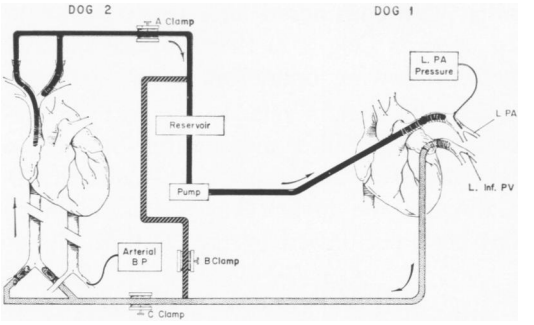


FIG. 5. The circuit for perfusing the left lower lobe *in situ* (Dog 1) with blood from a septic dog with peritonitis (Dog 2). The perfusion was started with normal blood employing the shunt. Subsequently the blood of the infected animal was introduced by closing the shunt (clamp B) and opening clamps A and C.

The pulmonary arterial perfusion pressure was recorded from a fine polyethylene cannula (0.04″ I.D.) passed distally into the inferior pulmonary artery via the stump of the upper lobe artery, connected to a pressure transducer (Statham p23BB) and thence to a continuously recording oscillograph (Visicorder, 1508, Honeywell). The systemic arterial blood pressures of both dogs were similarly measured by pressure transducers (Statham p23Db) connected to catheters inserted into the femoral arteries.

Acute peritonitis was induced in dogs by ligation of the cecum, accompanied by the intraperitoneal injection of a suspension of the animal's own enteric organisms in 20 ml. of normal saline. Penicillin (1,000,000 units) was given intramuscularly at the close of operation to prevent dissemination of *Clostridium welchii*. Of 21 dogs operated upon, four failed to survive for 24 hours. Of the survivors, only those dogs with rectal temperatures above 103.5° F. which exhibited evidence of acute perito-

nitis were considered sufficiently septic to be used as Dog 2 in these experiments 24 hours following operation.

**Statistical Analysis.** In the text and accompanying tables, mean values are given together with the appropriate standard deviation of the mean. Analysis of variance has been performed by the "t" test.

## Experimental Procedures

**Control Experiments.** To determine the effects of prolonged perfusion upon the isolated vasculature of the test lobe, four experiments were conducted in which both Dog 1 and Dog 2 were maintained in a normovolemic and nonseptic condition. Hemodynamic measurements were made at the outset of the experiment and again after continuous perfusion for 4 hours. Pressure-flow curves were constructed by recording the mean left pulmonary arterial pressure while raising the rate of perfusion by increments of 100 ml./min. over a range corresponding to 30% to 250% of the normal resting value. Between observations, perfusion was maintained at a rate calculated to be the normal resting flow (20 ml./Kg. body weight/min., approximately 22.5% of the resting cardiac output). Biopsies were taken of both the normal and perfused lungs of Dog 1 before the commencement of perfusion for comparison with others taken at the end of the procedure.

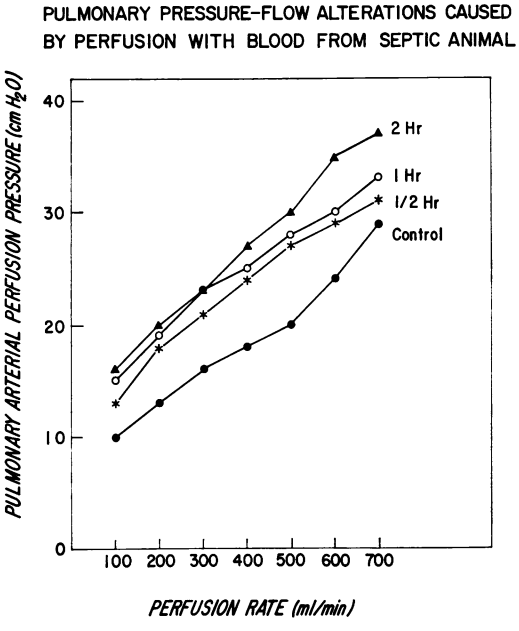


FIG. 6. The changes of pressure flow curves shown are typical of the entire series when blood from a septic animal was perfused through the test pulmonary lobe (Table 3).

**Experimental Acute Peritonitis.** (Continuous perfusion of the test lobe with acute peritonitis):

Using the bypass line of the preparation illustrated in Figure 5, a control pressure-flow curve was established immediately prior to the introduction into the circuit of a dog with acute experimental peritonitis (Dog 2). The bypass line was then clamped. The pressure-flow relationship was again determined after ½ hour, 1 hour and 2 hours of continuous perfusion at the calculated resting flow rate with the blood of the septic dog. A biopsy specimen was taken of the test lobe of Dog 1 prior to the inclusion of the septic dog into the circuit, and again after 2 hours of perfusion. A biopsy was also obtained of the lung of Dog 2 for comparison.

**Results: Control Experiments.** The mean pulmonary arterial perfusion pressures recorded at the commencement and termination of 4 hours of continuous perfusion with blood from a normal dog revealed no statistically significant change in mean perfusion pressure ($p < 0.75$).

The perfused lung of Dog 1 showed only minimal changes after 4 hours of continuous perfusion as illustrated in Figure 7. The septa were thin and the alveoli were polygonal in shape. Neither septal edema nor congestion were apparent, although there was a slight infiltration of the septa with mononuclear leukocytes.

### *Continuous Perfusion of the Test Lobe with the Blood of a Dog with Acute Peritonitis*

The pressure-flow curves obtained in a single experiment are shown in Figure 6.

TABLE 3. *Hemodynamic Alterations Caused by Continuous Perfusion of the Test Lobe with the Blood Circulating Through a Dog with Acute Peritonitis*

| | (7 Experiments) Mean Pulmonary Arterial Pressure (cm. $H_2O$) ± S.D. | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Normal Blood | | Acute Peritonitis | | | | | |
| Flow (ml./min.) | Control Pressure | S.D. | ½ Hour Pressure | S.D. | 1 Hour Pressure | S.D. | 2 Hours Pressure | S.D. |
| 100 | 12.5 | 2.6 | 15.5 | 2.4 | 15.8 | 2.0 | 16.1 | 2.8 |
| 200 | 15.4 | 2.7 | 19.0 | 2.4 | 20.7 | 3.7 | 20.5 | 3.7 |
| 300 | 18.1 | 3.1 | 22.0 | 3.6 | 22.4 | 3.1 | 24.2 | 4.6 |
| 400 | 20.0 | 3.3 | 25.1 | 4.5 | 25.4 | 3.9 | 28.1 | 5.6 |
| 500 | 22.2 | 3.8 | 28.5 | 5.7 | 29.1 | 5.3 | 31.8 | 6.6 |
| 600 | 24.4 | 4.5 | 32.0 | 5.8 | 33.0 | 5.5 | 36.0 | 7.9 |
| 700 | 29.7 | 4.7 | 35.1 | 7.2 | 36.4 | 6.5 | 39.1 | 8.4 |

n for each flow rate = 7.

The introduction into the extracorporeal perfusion circuit of Dog 2, in which acute peritonitis was induced 24 hours previously, leads to an elevation of pulmonary arterial perfusion pressure. This increase persists up to the termination of the experiment following 2 hours of perfusion.

The data obtained from seven such experiments are summarized in Table 3. The observed alterations in perfusion pressure have also been calculated above and below the initial values for each individual experiment. The means of these percentile differences are shown in Table 4.

Statistical analysis reveals that continuous perfusion of the isolated vascular bed of the lung with the blood of a dog in which acute experimental peritonitis has been produced 24 hours previously, leads to a progressive elevation of the perfusion pressure. This rose to 26.8% (±20.8) above the control value at one half hour, 29.9% (±17.5) at one hour, and 36.5% (±18.0) at two hours. Each is a statistically significant increase above the control value ($p < 0.001$).

Examination of the lung biopsy specimens revealed the following changes. Following 2 hours of perfusion with the blood of Dog 2, the perfused lobe of Dog 1 demonstrated edema of the alveolar septa, accompanied by massive invasion with polymorphonuclear leukocytes. These cells are also seen to adhere to the surface of the vascular endothelium. The alveolar capillaries are distended and packed tightly

TABLE 4. *Mean Percentage Change from Control of Pulmonary Arterial Perfusion Pressure*

| Flow (ml./min.) | ½ Hour % | S.D. | 1 Hour % | S.D. | 2 Hours % | S.D. |
|---|---|---|---|---|---|---|
| 100 | 32.4 | 26.2 | 25.2 | 20.1 | 31.0 | 21.9 |
| 200 | 28.4 | 23.5 | 26.1 | 18.5 | 35.0 | 21.8 |
| 300 | 25.1 | 21.0 | 25.0 | 15.0 | 34.5 | 17.6 |
| 400 | 27.2 | 20.2 | 28.0 | 15.5 | 41.1 | 18.1 |
| 500 | 27.4 | 19.0 | 30.5 | 15.5 | 42.0 | 18.6 |
| 600 | 25.4 | 20.4 | 27.7 | 20.1 | 39.8 | 18.7 |
| 700 | 21.2 | 22.7 | 25.1 | 23.8 | 32.4 | 21.0 |
| | Mean % change = 26.8 (20.8) | | Mean % change = 26.9 (17.5) | | Mean % change = 36.5 (18.9) | |
| | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ | |

n for each flow rate = 7.

with erythrocytes (Fig. 8). Areas of focal alveolar collapse are seen, close to larger pulmonary arteries and bronchi. In these same areas periarterial and peribronchial hemorrhage is evident. These changes are also found to be present, and equally extensive in the lungs of Dog 2 (Fig. 9). The remaining lung of Dog 1 (recipient) was morphologically normal at the end of two hours (Fig. 10).

## Discussion

The elevation of right ventricular pressure to values in excess of 35 mm. Hg in six of ten patients with severe peritonitis is strongly suggestive of pulmonary hypertension. Either left heart failure or an increase of pulmonary vascular resistance must be present. From the clinical studies presented here there is no direct evidence for or against left heart failure. The total periph-

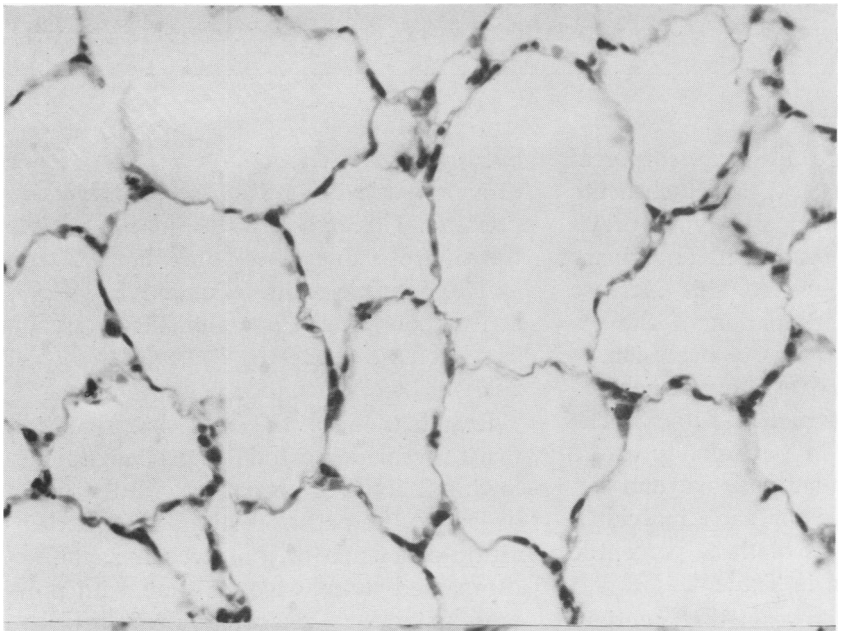

FIG. 7. The perfused lobe after recirculation of blood from a normal dog is morphologically normal. Note the thin septa and polygonal shape of the alveoli.

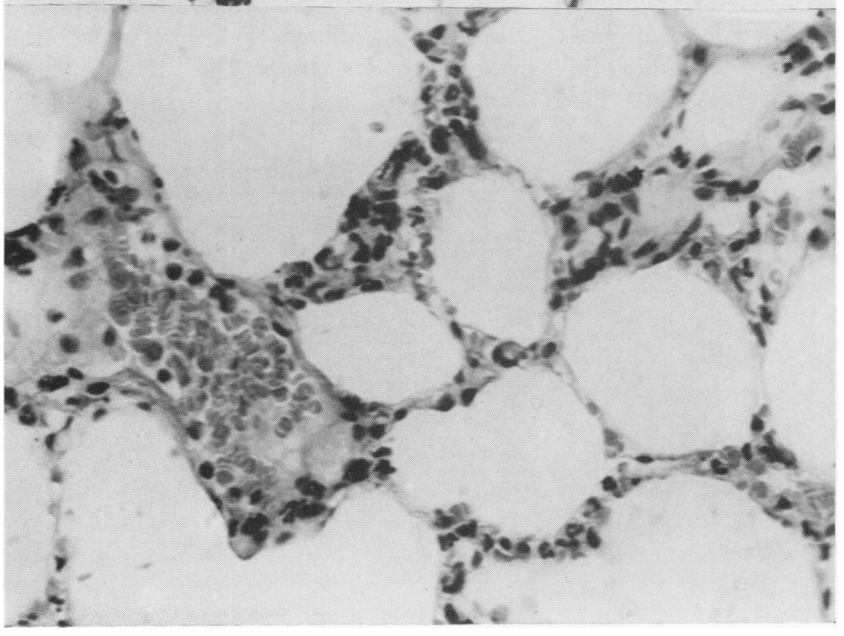

FIG. 8. The characteristic histological alterations of a biopsy of the test lobe after 2 hours of perfusion with blood circulating through a septic animal with peritonitis. Note the interstitial edema, intravascular congestion, margination and infiltration of leukocytes, and focal alveolar collapse.

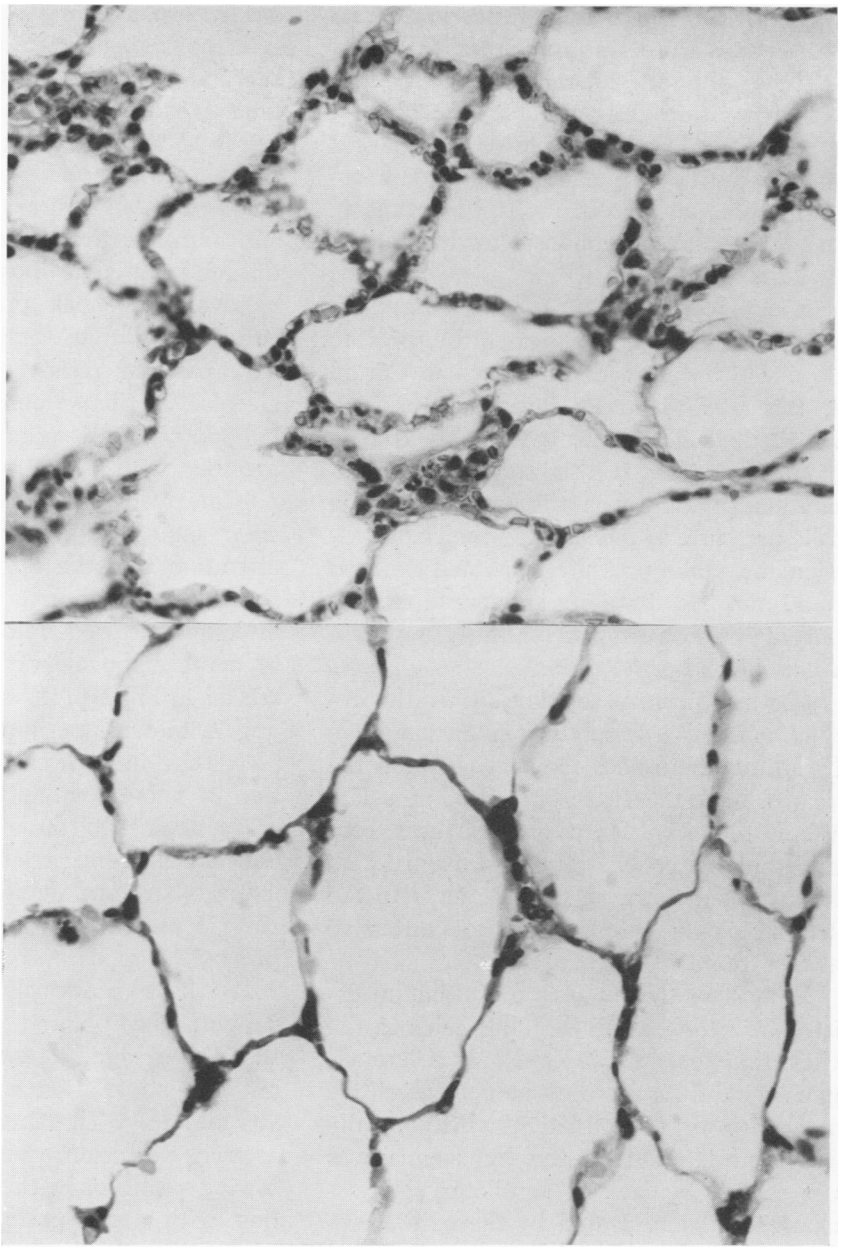

FIG. 9. The histological appearance of the lungs in the septic animal (Dog 2) exhibits the abnormalities typically found after 1 or 2 days in animals with induced peritonitis. They include interstitial edema, congestion, and alveolar collapse.

FIG. 10. The normal histological appearance of the remaining lung of the animal (Dog 1) bearing the test lobe. Only the dog's own normal blood was circulated through this lung. It remained unaffected by the blood circulation from the septic animal through the test lobe.

eral resistance is low in the presence of severe sepsis and the cardiac output is prone to be elevated.[6, 9, 25] In the terminal period both the cardiac output and the arterial blood pressure are low as shown in Table 2. These conditions should, in fact, relieve the left heart of strain. On the other hand there is little question that the increase of right atrial pressure from a normal value of 5 cm. $H_2O$ or less to 12 cm. $H_2O$ and subsequently to 19 cm. $H_2O$ is an indication of right heart failure.

A comparison of the data obtained from the conscious dogs with peritonitis given in Figure 3 with that from the patients in Figures 1 and 2 suggests that the animals behaved in almost every respect in a fashion similar to man. The low left atrial pres-

sures in the dogs leaves little doubt that left heart failure was not present. Assuming that the same hemodynamic pattern was present in the patients, it would appear that pulmonary hypertension plays a part in the development of right ventricular failure, and probably is important in the subsequent reduction of cardiac output in those who died.

A significant increase of pulmonary vascular resistance of 52% was present in the dogs which survived. As shown in Figure 4, this was markedly increased in those which died. The same is probably true in man. Especially is this true in the premortem period when the pulmonary systolic pressure, as reflected by the right ventricular systolic pressure, remained elevated to 40 mm. Hg despite a subnormal cardiac output which averaged for the group as a whole but 2.2 $L/M^2/min$.

Another striking relationship is the reduction of the arterial oxygen tension while breathing air in both the survivors and the deaths, respectively, to 62 and 53 mm. Hg. When the respiratory gas mixtures contained higher concentrations of oxygen with high oxygen tensions, the gradients to the arterial blood were even more impressive as illustrated in Figure 1.

In most of the patients this situation existed at a time when the lung fields in the chest radiographs exhibited only a "ground glass" or diffuse mottling but not extensive atelectasis or consolidation which usually appeared later. That the hypoxemia was not caused by lack of ventilatory gas exchange is demonstrated by the marked reduction of the arterial $P_{CO_2}$, a phenomenon which has been frequently noted.[11, 25] Therefore, it appears that this must be related to a reduction of the ventilation-perfusion ratio caused by focal alveolar collapse or an increase of dead space.

The problem is what the mechanism may be in the lung for the simultaneous development of hypoxemia and an increase of pulmonary vascular resistance. The latter appears to be in part responsible for inability of the circulatory system to maintain the high cardiac outputs essential for survival in patients who are suffering from widespread peritonitis or other extensive sepsis.[6, 9, 19]

The second series of experiments demonstrates that in acute sepsis hemodynamic and morphological changes are induced in the lung similar to those observed in acute hypovolemic shock previously reported.[10] In both conditions there is a rise in pulmonary vascular resistance, accompanied by alveolar capillary congestion within the lung and the development of septal edema, together with the apparent adherence of polymorphonuclear leukocytes to the vascular endothelium and their subsequent migration into the interstitial tissues. The microthrombi observed in biopsies taken of lungs perfused with the blood of dogs in acute hypovolemic shock are not observed in lungs perfused with the blood of dogs with acute peritonitis. The changes observed are in each case an exact reproduction of those seen in intact dogs.[11] They are not due to the effects of perfusion, which has been carried out for as long as 4 hours without significant change occurring in either perfusion pressure or morphological appearance.

We have previously given evidence to support the opinion of Fishman[20] that there is no significant direct effect of sympathetic stimulation upon the pulmonary vasculature.[13] The increase in pulmonary arterial perfusion pressure observed following perfusion with blood from either a dog with acute peritonitis, or a dog in acute hypovolemic shock appears to be due to substances in, or forming part of, the circulating blood. The histological studies which have been performed lead us to believe that this increase in pulmonary arterial pressure is related to the plugging of pulmonary arterioles and capillaries with tightly packed erythrocytes.

It is possible that the same change in the physical characteristics of the surface of the pulmonary vascular endothelium which

leads to the development of alveolar septal edema also affects the surfaces of the circulating erythrocytes, leukocytes, and platelets. This would account for the adherence of leukocytes and platelets to the vascular surface in these experiments. Similar adherence between circulating erythrocytes would result in intravascular aggregation. Red cell aggregation has been observed in patients with traumatic shock,[1, 24] and is considered by Begg and Hearns[5] to be among the most important determinants of blood viscosity. Hardaway[16] has demonstrated the occurrence of diffuse intravascular coagulation in hypovolemic shock and sepsis, and states that such intracapillary clotting uses up clotting factors and completely halts perfusion in the clotted vessels. In a recent discussion of the consumption coagulopathy which may accompany septicemic shock,[12] it has been suggested that the activation of Hageman factor by bacterial endotoxin may be the initiating event of such intravascular coagulation. The resulting acceleration of fibrinogen-fibrin conversion would lead to the increased liberation of fibrinopeptides. Studies with specific fibrinopeptides (bovine fibrinopeptide B and human fibrinopeptide A) have demonstrated that these substances given in minute concentrations to rabbits, dogs and lambs result in pulmonary hypertension, decreased effective pulmonary blood flow and decreased lung compliance.[4]

There is increasing evidence that kinins released during shock and sepsis may contribute to the development of the pulmonary lesion. Attar *et al.*[2] have shown that bradykinin is released in significant amounts in human shock, playing a significant role in aggravating plasma loss and maintaining the hypotensive state. Recently, Nagasawa *et al.*[30] have shown that bovine factor XII (Hageman factor) directly activates purified bovine plasma kallilreingen to the active proteolytic enzyme kallikrein. This, in turn releases bradykinin (kallidin 9) from its inactive precursor, plasma kininogen. The exact mechanism by which this nonpeptide produces peripheral vasodilators, the margination of polymorphonuclear leukocytes within vessels, and increased vascular permeability is at present unknown. Majno and Palade[27] have demonstrated that increased vascular permeability is due primarily to the effect upon the small vessels. A separation occurs of the junction between endothelial cells, similar to that observed in the electron microscopic studies of Teplitz[35] and Goodman.[15] These authors have described widening gaps between endothelial cells, enlarging to approximately 40 A., and thus permitting the diffusion of molecules of up to approximately 40,000 molecular weight.[21] The development of edema of the alveolar septa raises the possibility that an increase in pulmonary vascular permeability, as suggested by Swenson,[34] is responsible rather than of pulmonary arterial or venous spasm.

The margination of polymorphonuclear leukocytes within pulmonary arterioles demonstrated histologically in the present studies is of particular interest, since there is evidence that these cells contain an enzyme or enzymes capable of initiating the release of kinins from kininogens.[22]

Other possible biochemical mediators are the catecholamines, histamine, and serotonin. Although we have been unable to detect a direct effect of sympathetic nervous stimulation on pulmonary arterial pressure, it is possible that an indirect effect may be exerted by catecholamines released as a result of intense sympathetic stimulation elsewhere. The direct injection of 10 to 200 mg. of norepinephrine into the pulmonary artery of an isolated perfused dog lung has been shown to result in an elevation of both systolic and diastolic pressures.[20] However, this represents a concentration in excess of that observed in previous patient studies.[9]

Histamine, a potent peripheral vasodilator, is released from tissues damaged by anoxia and injury,[32] and has been shown to be present in markedly increased

amounts in the plasma of patients with gram-negative septicemia.[23] As Heineman and Fishman[17] have pointed out parenterally administered histamine causes an increase in the calculated pulmonary vascular resistance in intact dogs, but not in man. The effect on the pulmonary vasculature is rendered more complex since histamine increases the permeability of minute vessels and promotes the accumulation of fluid in perivascular spaces, leading to the compression of small vessels. An added source of histamine may be that released from the mast cells of the lung as a result of local damage. *In vitro* perfusion experiments have also demonstrated that when 5-hydroxytryptamine is added to the perfusate, histamine appears in the effluent perfusion fluid.[14] The platelet microthrombi observed in the pulmonary capillaries in hypovolemic shock (but not after perfusion with the blood of dogs with acute peritonitis) would appear to be a rich local source of serotonin (5-hydroxytryptamine). Aggregations of platelets may originate in injured or underperfused peripheral tissues and embolize to the lungs, or may be formed locally at the site of endothelial injury. The release of serotonin within the pulmonary capillaries from the degradation of damaged platelets may be a contributory factor in the development of the hemodynamic and morphological response of the lung to acute hypovolemic shock.

The increase in pulmonary arterial pressure which we have observed in hypovolemic shock and in acute sepsis appears to be due to mechanical interference with the free passage of blood through the pulmonary capillaries, apparently as a result of plugging of these vessels with erythrocytes. This rise of pulmonary vascular resistance is frequently reflected in clinical practice by a high central venous or pulmonary arterial pressure in patients with similar conditions,[10, 19] resulting in a degree of apparent right heart failure. The use of recordings of the central venous pressure to monitor the adequacy of blood or fluid replacement in patients with hypovolemic shock therefore becomes unreliable, since the pressure may be within the normal range well before adequate restoration of the circulating blood volume has been achieved.

A number of therapeutic considerations are suggested by these findings. Although a normal blood volume must be assured to permit the circulatory organs to maintain the high cardiac output required in the face of extensive sepsis, it would appear wise to avoid excessive use of isotonic or hypotonic crystalloid solutions. In a situation in which abnormal pulmonary vascular permeability and interstitial edema seems to be a feature, this type of solution containing readily diffusable ions should make the situation worse. This concept is born out by the observations of the wounded in Viet Nam by Proctor *et al.*[31] They found significantly less work of breathing and greater pulmonary compliance in patients treated with blood in preference to Ringer lactate solution. Skillman *et al.*[33] demonstrated an improvement in oxygen transmission by the lung in seriously sick patients when salt poor hypertonic albumen was given in conjunction with a diuretic. The improvement of the arterial blood $P_{O_2}$ following a diuresis in Case 2 of this series is illustrative of this effect.

The effectiveness of hydrocortisone is debatable, but it is possible that membrane permeability may be reduced with a reduction of the interstitial edema. Whether the production of surfactant in affected areas may be restored by reduction of edema or better perfusion is questionable. At times large doses of hydrocortisone appear temporarily to improve arterial oxygenation as in Case 1. Unfortunately, the preliminary results with hydrocortisone administration during pulmonary perfusion experiments fail to show any significant difference either in hemodynamic or morphological effects. Agents such as trasylol and other antagonists for proleolytic enzymes which release bradykinin have not proven helpful to date.

However, the search must be continued.

Digitalis, as illustrated in Figure 1, increased the cardiac output by an average of 18% in 12 patients and was accompanied by elevation of the arterial blood $P_{O_2}$ in seven. This drug should be administered whenever there is evidence of right heart failure or serious hypoxemia in the presence of severe sepsis.

Blocking the development of intravascular coagulation and aggregation of red cells might be accomplished with corticoids by altering erythrocyte surface membranes causing a reduction of the capillary "blocking." Employment of dextran or heparin suggest themselves. Unfortunately all of the perfusion experiments reported here were carried out with full heparinization. Probably the intravascular coagulation is initiated at the site of injury or infection regardless of the presence of heparin.

The use of respirators is helpful in restoring oxygenation and effective perfusion, but this is a wide field beyond the purview of this paper. Oxygen in excess of 50% must be avoided for prolonged periods, and the ventilatory gas mixture should be highly humidified.

Above all, elimination of the septic focus by surgical maneuvers or by chemotherapeutic agents is the treatment of choice in dealing with this pulmonary and circulatory problem.

## Summary

1) The results of clinical observations on 38 patients with generalized peritonitis are presented. Of these 16 died. Two animal experiments employing standardized peritonitis induced by cecal ligation are also presented to examine the relationship of circulatory insufficiency and failure of pulmonary oxygen transmission in the presence of severe nonthoracic sepsis.

2) During the acute phase of the disease the average right ventricular systolic pressure was 41 mm. Hg and remained elevated in those patients who subsequently died. The central venous pressure at the same time was 10 cm. $H_2O$, rising to 19 cm. $H_2O$ terminally when the cardiac index had fallen from 4.7 to 2.2 $L/M^2/min$. In dogs with peritonitis the same pulmonary hypertension was observed with the additional finding that left atrial pressure fell.

3) The pulmonary hypertension occurred at a time when hypoxemia (average arterial $P_{O_2}$ 58 mm. Hg) was present despite the absence of radiological evidence of atelectasis or widespread bronchopneumonia.

4) The mechanism of the hemodynamic and morphological changes were studied by perfusing normal dog lung *in situ* with blood circulating through a second normal or septic dog. In contrast to the normal blood that from the septic animal rapidly produced an average 36% elevation of the pulmonary vascular perfusion pressure. The essential features of the lesions, characteristic of the lung pathology previously described in septic man and animals are an interstitial edema, vascular congestion and focal alveolar collapse.

5) It is concluded that in severe nonthoracic sepsis hypoxemia (reduction of ventilation/perfusion ratio) may be accompanied by an increase of pulmonary vascular resistance and right heart failure. These hemodynamic and functional changes of the lung are caused by blood born elements which appear to increase capillary permeability and vascular blocking. Therapeutic measures are discussed relative to the maintenance of high cardiac output and normal blood volume without increasing pulmonary disorder. Excessive volumes of crystalloid are to be avoided. Rather plasma or salt-poor albumin are recommended. Digitalis has proven effective for improving both cardiac output and oxygen transmission by the lung.

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