ABSTRACT

CARDIOPULMONARY STUDIES IN CRITICAL ILLNESS:
Changes in Aspiration Pneumonitis.

Cardiopulmonary studies in eighteen patients with aspiration pneumonitis and thirteen patients with shock or sepsis have been correlated with routine laboratory, X-ray and pathologic findings.

The hypoxaemia and widened A-aDO_2 observed in aspiration pneumonitis improved with IPPV, suggesting maldistribution of ventilation compatible with pulmonary oedema. Progressive plasma volume loss averaging 500 ml. after 24 hours was associated with hypotension and was best corrected by careful replacement with colloid solutions. Cardiac failure only occured in patients with pre-existing heart disease or overtransfusion. The pneumonitis was initially non-infective; and antibiotics did not prevent subsequent pulmonary infection. The mortality was 40 percent in aspiration pneumonitis and 70 percent in shock and sepsis. Advanced age, pH of aspirated gastric contents below 1.75 , prolonged hypoxia and concurrent sepsis were the main factors associated with high mortality.

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CHAPTER 1. INTRODUCTION

Respiratory insufficiency is recognised with increasing frequency as a cause of death in critically ill patients with shock, trauma and sepsis (1-16). The exact cause is unknown; but clinical and experimental studies suggest that a common response of the lung may exist to tissue injury and infection; the important stimuli being low pulmonary blood flow , toxins and probably microthrombi.

Pulmonary insufficiency following hypovolaemic shock has been related to pulmonary hypoperfusion and to the specific effects on the lungs of impaired systemic perfusion. Pulmonary ischaemia is associated with greater structural and functional damage when the bronchial circulation is impaired (17) and when alveoli are collapsed rather than inflated (18). The finding by Henry et al. (19,20) of reduced uptake of phosphorus and reduced oxygen consumption of the lung tissue after resuscitation from experimental haemorrhagic shock is clear evidence of impaired metabolic activity in the ischaemic lung.

Structural pulmonary capillary damage and pulmonary oedema after administration of endotoxin or living bacteria has been documented repeatedly; and reported series of patients with

progressive pulmonary insufficiency consist largely of patients with major sepsis.

Clotting abnormalities may occur in shock .These include thrombocytopenia decreased plasma levels of fibrinogen and other clotting factors and appearance of fibrin degradation products and activated intermediate clotting factors .These changes are compatible with disseminated intravascular coagulation; and Hardaway (1), Blaisdell (9) and others have suggested that in shock, especially in the presence of severe tissue damage, disseminated intravascular coagulation provides an intermediary mechanism leading to pulmonary ischaemia and respiratory insufficiency.

Other factors may aggravate the primary insult. These include heart failure and overhydration (21 - 24), oxygen intoxication (25 - 34) and acid pulmonary aspiration.

Aspiration pneumonitis probably contributes more frequently to posttraumatic pulmonary insufficiency than is commonly realized (25,35,36). Much has been written on the acid pulmonary aspiration syndrome; but experimental studies demonstrating the haemodynamic pattern in aspiration pneumonitis are only recent ; and documentation of changes in haemodynamics and respiratory gas exchange in clinical patients has been scanty.

CHAPTER 2. HISTORICAL

Hippocrates recognised the danger of death from aspiration of food or fluid into the tracheobronchial tree (37). John Hunter described the effects of aspiration of brandy by cats, clearly recognizing that death was due to pulmonary aspiration (37). The first documented clinical case of aspiration pneumonitis was presented by James Simpson in 1848 (38) - though his colleagues considered it a case of chloroform overdose. The first reliable report of death due to aspiration of vomitus was in 1853 (38). Holscher, in 1898 related the finding of tracheal rales and lung infection after ether anaesthesia to aspiration of mouth secretions; and Applebach and co-workers in 1937 and 1940 described the pathology of aspiration pneumonitis ,(39). Except for cases of obvious asphyxiation little importance was attached at this time to aspiration of small quantities of liquid or solid material.

In his classical clinical and experimental study published in 1946, Mendelson established the role of gastric acid in the pathogenesis of the aspiration syndrome and differentiated the acid aspiration syndrome from solid particle aspiration (40). This treatise and that of Teaubeaut in 1952 (41) clarified the pathologic sequence of events following acid aspiration. Recent workers have added studies of haemodynamics and pulmonary function;

most of these have been experimental , and clinical reports have been of isolated or at most of four to six cases.

As treatment of the initial catastrophic events resulting from severe thermal burns has improved, pulmonary damage due to smoke and heat inhalation has been recognised with increasing frequency (42 - 48); and the remarkable clinical and pathologic similarity between aspiration pneumonitis and smoke inhalation pneumonitis has become apparent.

CHAPTER 3. INCIDENCE.

The overall incidence of aspiration pneumonitis is unknown, but in intubated supine patients undergoing elective operations it seems to be about 10% (49); and in patients undergoing non-elective operations this figure must be much higher. The overall incidence of death in patients following aspiration is placed at 14% by Bannister and Sattilaro (38). Several hundred cases have been reported since Mendelson's report, and many more have undoubtedly gone unrecorded; others which follow "silent" regurgitation may be undiagnosed. Culver and co-workers (50) examined the frequency of aspiration during nitrous oxide / ether anaesthesia in 300 patients, using Evans' Blue as indicator.He found regurgitation in 26% and aspiration in 16%. Regurgitation and aspiration were both more frequent when the patient was in the Trendelenberg position and when a nasogastric tube was not employed preoperatively. Berson and others (51) conducted a similar study in 926 patients. Food was withheld for eight hours prior to operation and Carmine red was used as the indicator. The overall frequency of regurgitation and aspiration was 14% and 7% respectively , but these rates were nearly doubled in difficult inductions.Endotracheal intubation without a cuff, absence of a nasogastric tube and the Trendelenberg position were all associated with increased incidence of regurgitation

and aspiration; and the highest incidence of regurgitation was found when ethylene was used as the anaesthetic agent. In all 66 cases of aspiration the postoperative course was uneventful, and no pneumonitis was observed clinically or radiologically. More recently Marshall and Gordon (39) studied the frequency of regurgitation in 219 surgical and obstetrical patients during anaesthesia . Seven percent vomited, 5% had silent regurgitation and 1% obvious regurgitation. Poor preparation and a full stomach were the commonest predisposing factors.

How often does failure to record an episode of possible aspiration lead to subsequent lack of recognition of aspiration pneumonitis? It is becoming increasingly apparent that the delicate balance of pulmonary ventilation/perfusion relationships in the critically ill patient may often be impaired by acid aspiration (36). Aspiration may follow vomiting or regurgitation in patients in whom the normal protective reflexes of glottic closure are impaired by age, debility, neuromuscular disorders, coma or intoxication or general anaesthesia (36, 52-54). Awareness that serious illness may provide just this setting, often in the patient who can least afford aspiration, should lead to precautions to avoid such an accident.

CHAPTER 4. PATHOPHYSIOLOGY

It seems that few patients who aspirate develop the clinical syndrome of aspiration pneumonitis (51).The most important determinants of the course following aspiration may be the amount, nature and pH of the fluid aspirated. In Mendelson's classical study of 66 patients (40), analysis of the aspirate was available in 45. Of these , 40 had liquid aspiration and 5 solid particle aspiration. Mendelson examined the effects of endotracheal instillation of 0.1N Hydrochloric acid, normal saline,liquid vomitus, and vomitus of solid food particles on rabbits.He concluded that solid particles produced mechanical obstruction and asphyxia or massive atelectasis ,while liquid was only effective in producing severe pneumonitis if it was acid. Subsequently, Teaubeaut (41) established the range of pH of aspirate (pH 1.5 to 2.4) which produced severe dose-related pneumonitis in dogs; and noted that it was the same as the normal range of pH of resting gastric juice in man. Gastric aspirate of pH greater than 2.4 obtained from healthy volunteers after dairy, meat, and vegetable diets ,produced miliary granulomatosis, and mild obstructive bronchiolitis , but no severe pneumonitis; whereas aspirate obtained after an alcohol diet had a pH lower than 2.4 and produced pneumonitis. Awe (53) compared the effects of 0.1N, 0.01N, and 0.001N Hydrochloric acid and aspirated tube-feeding on the lungs of intact dogs. Graded doses of 0.1N Hydrochloric acid

had the same effect in producing chemical pneumonitis. Tube-feeding produced mechanical airway obstruction rather than chemical pneumonitis, and the response was dose-related . Greenfield (55),however, found the mortality in dogs given graded doses of endotracheal 0.1N Hydrochloric acid to be related to the dose. With 1cc/kg. the mortality was nil; with 2cc/kg., the mortality was 50% in 24 hours; and with 3cc/kg., the mortality was 50% in 4 hours.

Experimental studies have revealed no evidence of infection by pathogenic organisms early in aspiration pneumonitis (41), and the early fever of aspiration is thought to be unrelated to infection. Bosomworth (56) and Hamelberg (37,57) produced severe pneumonitis in dogs which aspirated faecally contaminated gastric juice of pH 6.4, with a mortality of 100%. Boiling the contaminated gastric juice resulted in 100% survival, with only 5 days of morbidity. Aspiration of faecally contaminated gastric juice is therefore an incident of overwhelming seriousness; the resulting pneumonitis is probably infective from the onset. In Teaubeaut's experiments (41), Staphylococcus aureus, and various Gram-negative bacilli including Escherichia coli were cultured from the lung surfaces following aspiration of faecal vomitus. Clinical studies on the role of infection in aspiration pneumonitis have not been reported. In smoke inhalation pneumonitis ,Stone (43), found no evidence of infection at the onset, but all patients who survived more than 3 days developed pulmonary infection with Staphylococcus or Pseudomonas.

The pathologic lesion of aspiration pneumonitis resembles that of pulmonary oedema produced by chemicals duch as Alloxan. Pulmonary oedema results when the normal balance of broncho-alveolar transudation and reabsorption is disturbed. Reabsorption of alveolar fluid is a normal function of the lung (58). The pulmonary capillary pressure of healthy man which tends to filter fluid from the blood to the alveoli, is far less than the colloid osmotic pressure of the plasma proteins which tends to pull alveolar fluid into the blood. The imbalance prevents the transudation of fluid from the blood to the alveoli, and hastens the reabsorption of alveolar fluid into the blood. When tagged small molecules are dissolved in water and introduced into the alveoli, either by injection through a catheter or inhalation as an aerosol, they enter the circulation almost as rapidly and as completely as by intravenous injection. In 1873 Cohn reported that he introduced 25 litres of water into the trachea of a horse over a six hour period, and the respiratory tract absorbed the whole quantity without causing any apparent discomfort to the animal (59). Even large molecules such as that of albumin may be slowly absorbed intact from the alveoli directly into the pulmonary circulation as well as by the lymphatics (58, 60). Levine (61) in Fishman's laboratories , and Gaar and Guyton (22), have shown clearly the applicability of Starling's Law of trans-capillary exchange to the pulmonary capillaries. Fluid movement across the capillary wall is proportional to the sum ofcapillary hydrostatic and interstitial osmotic pressures minus the sum of interstitial hydrostatic and plasma colloid osmotic pressures.

Moreover, Clements (62), Levine and others have pointed out that as part of the recoil of the lungs derives from the operation of surface forces in the air spaces, the interstitial tissue pressure in the lungs depends on these surface forces. Increased alveolar surface tension may decrease the pericapillary pressure; thus, three pressures - capillary blood pressure, tissue fluid oncotic pressure and surface tensile pressure - tend to move fluid out of the capillary and into the alveoli. Normally these are balanced by the plasma oncotic pressure. Clements has attributed the increased egress of oedema fluid in the acute Respiratory Distress Syndrome of the newborn to increased alveolar surface tensile pressure (62).

	Plasma Oncotic Pressure		Capillary Blood Pressure		Tissue Fluid Oncotic Pressure		Surface Tensile Pressure
"Normal" Values	37	=	15	+	18	+	4
Acute RDS of the Newborn	37	<	15	+	18	+	4 to 30

The nature of the oedema fluid lost is related to structural damage of the alveolar capillary septum. Recent electron microscopy has aided the elucidation of the pathogenesis of pulmonary oedema in various conditions. The normal interalveolar septum consists of three layers: A layer of epithelial cells, mainly membranous but also granular, lining the alveoli and apposed by "tight" intercellular junctions of diameter about 8 Å ; a layer

of the basement membranes of the epithelial and alveolar cells, partly fused -thin segment - and partly separated from each other by an interstitial space containing collagen and elastic fibres - thick segment; and the endothelial cell layer with no "tight" junctions, the cells being separated by intercellular spaces of about 40 to 80 Å (63 -66). The collagen-containing septal interstitium may serve as a reservoir continuous with the perivascular and peribronchial interstitial space, with binding sites that may collect excess fluid caused by disparity between transudation and reabsorption. As the lung is second only to the skin in collagen content, this reservoir or "sponge" may play a significant role in keeping the alveoli dry (66, 67). When the "sponge" is overloaded the excess fluid collects in blebs between the endothelium and the basement membranes , and in the alveolar spaces. Desquamation of the endothelium and epithelium may occur, thus intensifying fluid accumulation in the alveoli. Histological evidence of overload of the reservoir and pulmonary oedema may be produced experimentally following aspiration of isotonic and hypertonic neutral solutions, as well as by acid aspiration (68,69). But acid potentiates the exudative reaction, by producing focal necrosis of endothelial and epithelial elements with a corresponding neutrophil response ; epithelial necrosis breaks the barrier that the "tight" epithelial cell junctions normally provide, permitting free and rapid passage of a protein rich exudate from the blood to the alveoli.

Arterial haemoglobin desaturation and cyanosis are well known features of aspiration pneumonitis, but complete clinical documentation of changes in pulmonary function has been scanty. Recent experiments have shown that the early changes are compatible with the effects of pulmonary oedema (53,55, 70, 37). Bosomworth and Hamelberg (37, 56) noted decreased arterial pH and decreased oxygen saturation despite oxygenation with 100% oxygen in dogs following aspiration of gastric juice. Awe (53) found the hypoxia and hypercarbia to be prompt and severe in solid food particle aspiration; while hypercarbia and acidemia were more modest in acid aspiration. Greenfield noted early hyperventilation and respiratory alkalosis in dogs given 1cc /kg., of 0.1N Hydrochloric acid endotracheally; those given 2cc /kg., often had early acidemia and hypercarbia; while acidemia and hypercarbia were most marked in those given 3cc/kg., hypoxemia was also more marked as the dose of endotracheal instillate increased.Hamelberg and Bosomworth (37) recorded a significant drop in tidal volume during spontaneous ventilation of dogs with aspiration pneumonitis ; and this was associated with a rise in P_{CO2} to an average of 50 to 60 mm Hg., indicating the need for ventilatory support. Apnoea of varying duration and uncertain cause sometimes occured . Fisk (70) studied respiratory gas exchange in isolated perfused dogs lungs, and found markedly decreased arteriovenous difference of P_{O_2} ,P_{CO_2} , and pH following endobronchial instillation of solutions of pH 1.2 to 2.4, but not with saline or solutions of higher pH . Recently clinical

cases have been reported (25, 35, 71) demonstrating marked hypoxemia and increased venous admixture.

Experimental studies of respiratory mechanics by Greenfield (55) and others (37, 72) have shown a decrease in lung compliance and in alveolar surfactant formation; though Brown (73) using a smaller dose of gastric juice in rabbits found no intereference in the action of alveolar surfactant.

Because of the similarity in clinical presentation between aspiration pneumonitis and pulmonary oedema of cardiac aetiology, it has long been presumed that in aspiration pneumonitis heart failure is induced by myocardial hypoxia; and venesection, rotating tourniquets, rigorous fluid restriction , digitalis and diuretics have therefore been used in treatment .Welch,in 1878, recognised that alterations in osmotic pressure, changes in the capillary endothelium and interference with lymph absorption might play a role in the genesis of pulmonary oedema, but found "great difficulty in conceiving any of these factors alone to be the cause of acute general edema of the lungs"; and proposed instead "A disproportion between the working power of the left ventricle and the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart" (74). In Visscher's opinion (74), "The Welch view will undoubtedly stand as the most perspicacious insight into the mechanism of the

commoner varieties of lung edema"; and more recently"of course, in the intact animal hypoxia leaves pulmonary edema, but this is related to the heart failure that hypoxia induces "(75).

Hypoxia is a well known myocardial depressant (76).For any organ, the margins of safety in hypoxia depend on its oxygen feserves and on its specific tolerance of hypoxia. The coronary arteriovenous oxygen content difference is normally so large that the heart can extract almost no additional oxygen on demand,that is, it has practically no oxygen reserves (77).

If Total Oxygen Content = 20 volumes%

and, Critical Capillary Oxygen Content = 7 to 11 vol.% (say, 9 vol.%)

then, Oxygen reserve of the Heart = (20 - 11.5)- 9 = nil.

The heart is second only to the brain in individual organ susceptibility to hypoxia; moreover, its oxygen requirement is increased eight-fold in systole. But cardiac output normally increases in hypoxia as part of the compensatory autonomic circulatory response; and redistribution of blood flow results in a disproportionate increase in blood flow to vital organs, the percentage increase in coronary flow being greater than that to any other organ. Since the circulatory gradient of oxygen tension -the arteriovenous oxygen content difference- is inversely proportional to blood flow the compensatory circulatory response to hypoxia effects a reduction in coronary arteriovenous oxygen

content difference. Thus the oxygen reserve of the heart may be increased. If the coronary blood flow cannot be increased , the coronary arteriovenous oxygen content difference becomes widened slightly, myocardial oxygen demand exceeds supply, and myocardial tissue hypoxia causes decreased cardiac output, and hypotension. In Keys' major study on the circulatory response to acute anoxia in man, the limit for increase of cardiac output was found at an arterial oxygen saturation of 73% the increased output being predominantly due to increased heart rate (78).

Awe (53) recently suggested on the basis of experimental data that acid aspiration produces a chemical pneumonitis analogous to a cutaneous thermal burn; and that the resulting plasma loss into the lung produces hypovolaemia with consequent progressive decline of cardiac output, systemic arterial pressure , right atrial pressure and blood volume and a corresponding rise of haematocrit and lung weight. Left atrial pressure remained normal. 0.1N Hydrochloric acid produced a 27% increase in haematocrit , a 35% decrease in plasma volume and a 26% increase in lung weight ; 0.001N Hydrochloric acid produced an 8% increase in haematocrit, a 7% decrease in plasma volume and a 13% increase in lung weight; while normal saline increased haematocrit by 3%, decreased plasma volume by 15%, and increased lung weight by 13%. No similar changes were noted following tube-feed aspiration. It followed that the restrictive measures used in pulmonary oedema of cardiac cause might in fact worsen the patient with aspiration pneumonitis by increasing the hypovolemia; and Awe advocated volume

replacement instead. Greenfield (55) confirmed the changes in haematocrit and lung weight following acid aspiration but did not observe progressive change with increased volume of aspirate. Cardiac output decreased as haematocrit and lung weight increased. An isolated clinical report (35) has recently supported Awe's view.

Pulmonary arterial hypertension has been noted in experimental aspiration pneumonitis (53,55,70,79,37) but has usually been left unexplained or else attributed to the pulmonary vasoconstriction associated with hypovolaemia (80).The studies of Colebatch and Halmagyi (72) suggested that fluid aspiration evokes a response of the parasympathetic nervous system, with both central and peripheral components, producing closure of lung units; Prostigmine intensified the response while atropinisation and prior vagotomy diminished it. A direct effect of aspirated gastric juice has also been demonstrated using the isolated perfused ventilated lung (70). Hypoxia is a well known potent pulmonary vasoconstrictor (76, 81-85) and its effect may be augmented by acidosis (81,82,86,87). The mechanism appears to be a direct effect on the arterioles (85). Moreover hypoxia may aggravate pulmonary oedema of other causes by increasing pulmonary capillary permeability or by pulmonary venoconstriction (74,88-92). Fishman doubts this (93,94),as he can find no evidence of muscle in the smaller precapillary venules or arterioles; only the larger precapillary arterioles 100 to 1000 microns in diameter - at the level of the respiratory bronchiole - are well equipped with muscle for vasomotor activity.Their corresponding venules

are poor in muscle. The pulmonary hypertension seen early in experimental aspiration pneumonitis is best explained by the arteriolar response to hypoxia and acidosis.Further, the hypocapnia associated with respiratory alkalosis in moderately severe cases may contribute to the increased airway resistance and decreased lung compliance observed in similar clinical situations (44,95-97). The effects of hypocapnia on airway resistance have been demonstrated clearly in animal experiments (96).

Purpose.

We have performed cardiopulmonary studies in patients with aspiration pneumonitis and in patients with shock or sepsis to elucidate :-

1. The significance of pH of aspirate in the clinical course of aspiration pneumonitis.
2. The pattern of respiratory gas exchange.
3. The relative roles of cardiac failure and hypovolaemia in the pathogenesis of aspiration pneumonitis.
4. The specific significance of aspiration pneumonitis in the critically ill patient.
5. The role of infection in the syndrome.
6. The effect of hypoxia on the pulmonary circulation in the development of aspiration pneumonitis.

CHAPTER 5. METHODS

Patients and Procedure.

Eighteen patients with aspiration pneumonitis have been studied from the time of admission to the Intensive Care Unit of the Montreal General Hospital.The diagnosis of aspiration pneumonitis was made on the basis of observed aspiration of gastric contents with symptoms of respiratory distress;or a history suggestive of aspiration followed by definite compatible clinical and radiological signs of pneumonitis . Frequent serial cardiopulmonary observations were made in the first 48 hours and as often as indicated thereafter. Clinical observations of pulse, blood pressure, respiratory rate , temperature and fluid intake and output were made. Serial microhaematocrits were done during the first 48 hours.Routine haematology and blood chemistry were obtained as indicated, and serial chest X-rays,ECG's, blood and sputum cultures done as often as necessary. Patient treatment was not standardised.Each clinician employed his own regimen in conjunction with the resident staff of the Intensive Care Unit; but practically all patients received oxygen, tracheal suction and ventilatory support, steroids,prophylactic antibiotics and intravenous fluid. All patients were cared for by Nurses trained in the management of seriously ill patients.

pH of Gastric Aspirate. When the patient was first seen, a nasogastric tube was inserted and gastric contents aspirated for measurement of pH.

Haemodynamic Measurements. A central venous catheter was inserted in most cases by percutaneous venous puncture or by venous cut-down; and correct placement was confirmed radiographically or by intracardiac ECG (98). Central venous pressure was measured with a simple saline manometer, using the midaxillary line with the patients supine as zero for the right atrium. Cardiac output and blood volume were measured at the outset and repeated in 24 hours. Cardiac output was measured by the indicator dilution technique. A Cournand needle was introduced percutaneously into the brachial or femoral artery or a radial artery cut-down was performed and a polyethylene catheter inserted. Indocyanine Green was the dye used. After injection of the dye into the central venous catheter arterial blood was withdrawn at a constant rate by means of a Harvard pump through a Gilford 103 densitometer, and the dye dilution curve was recorded simultaneously. Cardiac output was then calculated by the method of Hamilton (99) : The effects of recirculation were eliminated by replotting the exponentially decaying part of the dye curve on semilog paper, and the line obtained extrapolated to a low dye concentration; numerical integration was then performed by simple summation of successive ordinates placed at 1 second intervals ; finally the cardiac output was calculated as follows :-

$$\text{Cardiac Output (L./min.)} = \text{Calibration Factor} \times 60 \times \frac{\text{Mass of dye injected}}{\text{Area under Curve}}$$

The Calibration Factor was determined on each occasion. The arterial connections and densitometer cuvette were sterilised before use to permit reinfusion of blood. Cardiac output determinations were done in duplicate at 5 to 10 minute intervals and the mean of the two results taken .The mean arterial blood pressure, cardiac index and total peripheral resistance were calculated as follows:-

$$\text{Mean Blood Pressure} = \text{Diastolic Pressure} + \tfrac{1}{3}\,\text{Pulse Pressure}\ \text{(mm.Hg.)}$$

$$\text{Total Peripheral Resistance} = \frac{\text{Mean Blood Pressure} \times 1332 \times 60}{\text{Cardiac Output (ml./min.)}}\ \text{dynes/sec./cm.}^5$$

$$\text{Cardiac Index} = \frac{\text{Cardiac Output (L/min.)}}{\text{Body Surface Area}}\ \text{L./m}^2\ \text{/ min.}$$

Blood volume was measured by Radio-iodinated-serum-albumin (RISA) dilution, using the "Volemetron". The central microhaematocrit was determined simultaneously.Plasma volume deficits were calculated on the basis of measured blood volume haematocrit changes by the method of Moore (101).When the normal blood volume was unavailable,it was predicted as percent of body weight (100,102).

In one patient the central venous catheter was advanced into the right ventricle.Right ventricular pressure was measured by means of a Statham transducer and was recorded simultaneously on a Sanborn pressure recorder. The zero pressure reference was again the midaxillary line with patient supine. Right ventricular pressures were recorded in this patient who was breathing spontaneously before and after oxygenation with 100% oxygen using a tightly fitting face-mask. Arterial oxygen saturation was measured spectrophotometrically before and after full oxygenation.

Blood Gases and pH. Arterial blood was collected in a heparinised glass syringe , placed in ice chips immediately and analysed within 30 minutes of collection. Arterial P_{O_2} ,P_{CO_2} , and pH were determined at least daily using an Instrumentation Laboratory Blood Gas Analyzer ; and the alveolar-arterial oxygen difference $(A\text{-}aDO_2)$was obtained after the patient had breathed 100% oxygen for 15 to 30 minutes. Alveolar oxygen tension (P_{AO_2}) during 100% oxygenation was calculated from the barometric pressure (P_B) , water vapour pressure at body temperature (P_{H_2O}) and arterial P_{CO_2} , the latter being presumed to be equal to the alveolar P_{CO_2} (95,103), using the simplified alveolar gas equation.

$$P_{A_{O_2}} = P_B - P_{H_2O} - P_{CO_2}$$

Compliance. Total dynamic lung-thoracic cage compliances have been measured serially in some patients . The peak inspiratory

airway pressure (end-tidal pressure) was that recorded while on the Bird Mark 7 or Bennett ventilator.Tidal volume was calculated from the respiratory frequency and minute volume, the latter being measured by means of a Wright respirometer connected to the expiratory tube of the ventilator. No correction was made for compression of expired gas or expansion of the expiratory tube.

For comparison with results obtained in the patients with aspiration pneumonitis cardiopulmonary data obtained in similar studies performed in 13 seriously ill patients with shock or severe sepsis and respiratory distress have been documented here. Shock was defined for purposes of the study as hypotension of 70 mm.Hg. systolic or less, with clinical evidence of decreased tissue perfusion.

CHAPTER 6. RESULTS.

Patients with Aspiration Pneumonitis.

In 18 patients, 25 episodes of acid aspiration were noted and smoke inhalation was observed in 1 patient. The average age of the patients was 52.2 years (range 15 to 86 years) and 11 of the 18 patients were beyond the fifth decade. The major reasons for aspiration are shown in Table I . Coma or semicoma was the reason for aspiration in 7 patients 3 of whom had neurological disease. Six patients had gastrointestinal ileus ; some of these had received oral feeding prematurely , others had faulty or inadequate nasogastric drainage. In 4 patients aspiration occured in the perianaesthetic period.

Nature of Aspirate. Aspirate was unavailable for study in 8 patients. The pH of the aspirate was 2.4 or greater in 2, and less in the remainder. In none of these was the pH less than 1.2; four patients had pH less than 1.75 and in 4 the pH ranged from 1.75 to 2.4 . In one patient the aspirate was faeculent .One patient had a Zenker's diverticulum of moderate size in which regurgitated gastric contents accumulated and became infected before discharging into the respiratory tract. On three occasions we observed unequivocal aspiration of material of pH greater than 2.4 without subsequent development of pneumonitis recognisable by change in blood gases , chest X-ray or clinical status.

The relationships between pH of aspirate , lowest P_{O_2} and mortality are shown in Table II. One patient with aspirate of pH greater than 2.4 died but this followed the development of a large lung abscess rather than a severe pneumonitis. The mean lowest P_{O_2} was no different in patients with aspirate of pH 1.2 to 1.75 from that in patients with aspirate of pH 1.75 to 2.4; but all patients in the former group died (mortality 100%) whereas all but one in the latter group survived (mortality 25%). This was the patient with the Zenker's diverticulum referred to above.

Haemodynamic Changes : Changes in Plasma Volume and Blood Pressure. The maximal change in plasma volume as indicated by elevation of haematocrit frequently occured at or prior to the time the patient is first seen. In 7 patients plasma volume changes could not be assessed meaningfully because of concurrent blood loss or administration . Of the others, plasma volume deficits were less than 500ml. in 4 patients, 500 to 1000 ml. in 6 patients and greater than 1000 ml. in one patient. The relationship of plasma volume deficit to change in the mean blood pressure is shown in Table III. The immediate change in blood pressure correlates poorly with the plasma volume deficits. However, after 12 hours the fall in mean blood pressure is more marked in those patients with a moderate plasma volume loss (500 to 1000 ml.) and is greatest in the patient with the largest plasma volume deficit.

Changes in Cardiac Output. Cardiac output was measured on eleven occasions. The uniformity of the method of cardiac output determination was reflected in the close correlation between the results of the first and second of duplicate determinations. The cardiac indices at the outset and after 24 hours are shown in Table IV.The cardiac index was normal or high in 4 patients and low in one patient , Of the two patients with cardiac indices greater than 3.5 L/min./m^2 , one had cirrhosis and the other had concurrent sepsis. The only patient with a cardiac index less than 2.5 L/min./m^2 was in late septic shock .In every patient except this one, the cardiac index had increased somewhat when repeated after 24 hours.

Central Venous Pressure (CVP) was measured in 12 patients. The relationships of changes in CVP, cardiac index and total peripheral resistance are shown in Table IV , and a survey of CVP levels in all 12 patients is given in Table VI. In 7 patients the CVP did not rise above 10 cm. of water in the first 48 hours .In 4 patients it was more than 10cm.of water : Two of these had previous myocardial infarction and atrial fibrillation ; one had known atherosclerotic heart disease with clinical congestive heart failure prior to aspiration which was worse following aspiration; and one patient was overtransfused. In this patient and in one other with an elevated CVP tracheostomy was followed by a dramatic fall in CVP to within normal limits .In two patients the CVP rose above 10cm. of water after the second day.Both were overtransfused .One patient who was

already in positive fluid balance because of excessive fluid administration during a 16 hour period of marked oliguria received a further 4000ml. of blood and crystalloid fluid in excess of output during recovery . The other patient developed arrhythmia with a tachycardia of 150 beats per minute following administration of Propantheline, and then was overloaded with intravenous fluids; after digitilisation he reverted to sinus rhythm and a normal pulse rate and his CVP returned to normal levels. In one patient (Table V) a right ventricular systolic pressure of 59 mm.Hg associated with an arterial oxygen saturation of 76% fell to 34 mm.Hg.when the saturation was increased to 98% by breathing oxygen.

ECG Changes. The commonest electrocardiographic change observed was sinus tachycardia; but premature atrial and ventricular beats were also frequent.In some patients these disappeared during 100% oxygen breathing .Of the 4 patients with elevated CVP in the first 48 hours there were associated ECG changes in 3 independently reported as indicating progressively worsening myocardial ischaemia ; and in 2 who survived the ECG pattern improved as the patients recovered .One patient showed signs of right axis deviation and right ventricular strain during the hypoxaemic episode.

Respiratory Gas Exchange. The blood gas and pH changes are summarised in Table VI . The usual pattern was hypoxaemia with increased venous admixture .The lowest arterial P_{O_2} in the course

of illness was less than 50 mm.Hg in 14 of the 18 patients. The A-a DO_2, available in 11 patients after 15 minutes oxygenation with 100% oxygen, was greater than 600 mm.Hg in 3 patients, 500 to 600 mm.Hg. in 3 patients, and 300 to 400 mm.Hg. in 4 patients. In one patient the A-a difference was not determined during the period of greatest hypoxaemia and when determined after 24 hours treatment it was 205 mm.Hg. The widest A-a difference occured in those patients with aspiration pneumonitis who were given large volumes of non-colloid fluids.

The A-a difference decreased following Intermittent Positive Pressure Ventilation with oxygen; but in 3 patients the improvement was small or the A-a difference widened with progression of the disease despite this treatment until Continuous Positive Pressure Ventilation (Expiratory Positive Pressure) of 5 to 10 cm. of water was added. Two of these patients had been overtransfused ; fluid restriction was imposed simultaneously with institution of Expiratory Positive Pressure and diuresis accompanied resolution of pneumonitis . The changes in A-a difference correlated well with independently reported changes in radiological evidence of pulmonary infiltration; but less satisfactorily with auscultatory findings on clinical examination of the chest. Breath sounds were invariably diminished when the A-a difference widened markedly , but appreciation of clinical signs associated with smaller alterations in A-a difference was difficult.

In 5 patients hypoxaemia was initially accompanied by moderate or severe acidosis which responded readily to treatment. Hypercarbia was observed in 12 patients only 6 of whom had chronic obstructive lung disease; and 4 of these developed moderate or severe respiratory acidosis at the onset of illness . The remaining patients had respiratory alkalosis at the outset. Those patients with metabolic acidosis initially , also developed respiratory alkalosis when the acidosis was corrected.

Compliance. Table VII lists compliances measured at the period of most severe pneumonitis and during improvement or recovery. Dynamic total lung-thoracic compliances measured during the period of pneumonitis ranged from 0.014 to 0.044 L/cm. of water. The compliance fell during the period of deterioration of blood gas and clinical findings ,tending to precede the latter; and increased as these improved ,though it lagged behind them in doing so. In patients with sustained hypoxaemia, compliances remained low despite improvement of the A-a difference with treatment. The values in Table VIII taken from the course of patients Nos. 11 and 15 illustrate some of these points.

Pulmonary Infection. Sputum culture results at the onset of pneumonitis and subsequently are listed in Table IX. Sputum culture at the onset of illness was not available in 5 patients. Of the other 13 patients the initial sputum culture was negative in 9 and positive in 4. All patients with sputum positive at the

onset of pneumonitis had been hospitalised for some time prior to aspiration. The organism was D. pneumoniae in 1 and Gram-negative in 3 . All but 3 patients developed pulmonary infection subsequently . In 5 Staphylococcus aureus was the infecting organism ; in 6 it was a Gram-negative bacillus - Escherichia sp., Pseudomonas, Proteus sp. , Aerobacter or Paracolon sp. - but 2 of these had Gram-negative sputum infection before aspiration. Three patients developed mixed Gram-negative and Gram-positive pulmonary infections , 2 of these having been infected from the onset of illness.One patient developed a Pneumococcal pulmonary infection.

Prophylactic antibiotics were given in all but 3 patients, the commonest ones used being Penicillin ,Cephaloridine, Ampicillin, Cloxacillin and Kanamycin. They did not prevent subsequent infections in 13 patients. In some patients, one or more organisms cultured subsequently were resistant to the antibiotics that had been given. In 2 patients who received prophylactic antibiotics the sputum remained free of infection . Table IX summarises these results.

Pathology . Autopsy material or surgical specimens were available for gross and histologic examinations in 5 patients, and all confirmed the presence of aspiration pneumonia .The lungs were heavy, weights ranging from 520 grams in a 40 kg. patient with resolving aspiration pneumonitis who died due to a cerebrovascular accident , to 2730 grams in a 75 kg. patient with severe

recurrent aspiration pneumonitis. The lungs were firm and congested. The cut surface showed focal areas of pneumonic change; multiple abscesses were present in 2 patients and incipient abscess formation in another. Microscopically there were extensive areas of atelectasis and patchy necrosis. Exudative changes were widespread- the walls of alveoli and alveolar ducts lined by prominent fibrin hyaline membranes ; the alveolar lumen contained proteinaceous material infiltrated with polymorphs and mononuclear cells. Aspirated vegetable material was occasionally visible with a surrounding giant cell reaction. In some areas there was marked organisation of the exudate with deposition of reticulin fibres. Scattered proliferative epithelial changes were also present. The pulmonary arterioles showed some thickening but clear evidence of medial hypertrophy was lacking .Vascular congestion and dilatation were common .These changes are shown in the appended photomicrographs.

Mortality. Tables X and XI list data on mortality. Ten (55.5%) of the eighteen patients died, seven (39%) as a direct consequence of aspiration pneumonia. In three other patients (16.5%) aspiration was a significant contributory cause of death. The mean age of the survivors was 34.6 years while that of those who succumbed was 70.6 years. The mean duration of hypoxaemia in the survivors (5.6 days) was only half as long as that in those who died (12 days); but the mean lowest arterial P_{O_2} was similar in both groups ,(46.6 mm.Hg. and 43.1 mm.Hg.respectively).

Pulmonary sepsis occured in all those who died and was slightly less frequent in the survivors. Of the deaths six , (60%) had concurrent wound sepsis or peritoneal soiling, whereas only three (37.5%) of the survivors had concurrent sepsis.

Patients with Shock or Sepsis.

Thirteen patients were studied,4 with haemmorhagic shock, and 9 with severe sepsis 5 of whom were in septic shock and 1 in hypovolaemic shock. The average age of the patients was 71.7 years (range 55 to 87 years). The usual resuscitation began with blood volume replacement using whole blood,plasma and crystalloid solutions. When the central venous pressure rose above 12 to 15 cm. of water before restoration of tissue perfusion as indicated by clinical and laboratory signs, the patient was digitalised and sometimes intravenous Isoproterenol was added. In some patients steroids were given. Phenoxybenzamine was used in selected patients with septic shock who had decreased cutaneous perfusion and impaired renal function, in an effort to restore renal blood flow.

Haemodynamic Changes. In 13 patients cardiac output was determined on 41 occasions .As in the patients with aspiration pneumonitis duplicate determinations were done on each occasion, with good correlation between the first and second determinations. Pertinent data are shown in Table XII . In the patients with haemorrhagic shock the initial cardiac index was low and failed to show sustained improvement except in the patients who survived. This was associated with an increased total peripheral resistance. Central venous pressure rose above 10 cm. of water in 2 patients both of whom had established atherosclerotic heart disease. The cardiac indices in the patients with sepsis were normal or high except in one patient (# 7) who was in late septic shock

when first seen , and in another (# 11) who was severely hypovolaemic .Following volume replacement the latter patient went into heart failure, but when this had been treated the cardiac index was restored to normal levels. The pattern of increased cardiac index with low total peripheral resistance was seen commonly in the patients with sepsis.The survivors could not however be separated from those who died on the basis of the cardiac index.

Respiratory Gas Exchange. The blood gas and pH changes are summarised in Table XIII .The levels of hypoxaemia and increased A-a difference seen were similar to those in the patients with aspiration pneumonitis. All 4 patients with haemorrhagic shock initially had mild or moderate partially compensated metabolic acidosis resulting from decreased tissue perfusion, and without significant hypoxaemia .By the time hypoxaemia developed respiratory alkalosis was the usual pattern. The patients with septic shock presented in respiratory alkalosis except for 2 who had partially compensated metabolic acidosis; one was in late septic shock and the other was hypovolaemic .The same pattern was observed in the patients who had peritonitis but were not in shock.

Compliance . Total dynamic lung thoracic compliances measured in some patients , ranged from 0.02 L/cm. of water to 0.034 L/cm. of water at the time of maximal pulmonary insufficiency. As in the patients with aspiration pneumonitis compliances fell before deterioration of clinical and blood gas findings .

Pathology. Autopsy material was available in 4 patients. Bacterial pneumonia was present in all; in 2 it was severe organising pneumonia and was a major cause of death; two patients had focal bronchopneumonia , one of whom had diffuse interstitial and alveolar pulmonary oedema. The histologic appearances were similar to those seen in the patients with aspiration pneumonitis, but epithelial necrosis and hyaline membrane formation were not seen.

Mortality. Nine of the 13 patients died - an overall mortality of 69.2%. Three of the four patients with haemorrhagic shock (75%) died; and 6 of the 9 patients with severe sepsis (66.6%) died. Five of these were in septic shock.

CHAPTER 7. DISCUSSION.

Aspiration Pneumonitis is a serious complication in the critically ill patient . Recognition of aspiration as a contributory cause of unexplained respiratory insufficiency is important in the management of these problems.

The wide age range of the patients with aspiration pneumonitis illustrates that no age group is exempt from the risk of aspiration. Mental obtundity in children and young adults due to neurological disease, drug intoxication ,or serious illness predisposes to aspiration. Even healthy elderly patients may have diminished protective airway reflexes (54). Serious illness depresses these still further and may also inhibit gastrointestinal motility,thus setting the stage for aspiration of gastric contents. Previous studies have shown that neurological disease particularly cerebrovascular accidents provides the commonest setting for aspiration (53). The critically ill, but salvageable patient provides an equally favourable and more critical setting for aspiration.

Nature of Aspirated Gastric Contents. Other workers have advocated that pH be determined in patients with aspiration pneumonitis on pharyngeal and tracheal aspirate rather than on gastric aspirate (37, 71); but Awe (53) in his experimental study noted that the pH of tracheobronchial secretions rose rapidly

as massive blood-tinged proteinaceous fluid was exuded following aspiration. We have not attempted to test this finding clinically; instead we have obtained gastric aspirate by nasogastric suction upon first seeing the patient and have determined the pH of this fluid. Hamelberg and Bosomworth (37, 57) found that when the pH of gastric aspirate instilled endotracheally was below 1.2 the mortality of aspiration pneumonitis was 100% ; instillation of gastric aspirate of pH 1.75 or higher carried no mortality but significant morbidity. In the present series the mortality in patients with aspirate of pH 1.2 to 1.75 was 100% ; whereas that in patients with aspirate 1.75 to 2.4 was only 25 %. This finding confirms clinically the experimental evidence of the importance of pH of aspirate in the development and prognosis of ensuing pneumonitis ; and suggests that determination of pH of gastric aspirate in patients immediately postaspiration is an important guide in assessing prognosis.

Haemodynamic Changes. The plasma volume deficits recorded in patients with aspiration pneumonitis have been moderate.The technique of measurement of plasma volume deficits would have been improved by separate measurement of plasma volume with RISA and red cell volume using type O-negative red blood cells tagged with radiochromate - 51 ; an additional refinement is the use of a multiple sampling technique with extrapolation to zero time to reduce errors of mixing. However, the method employed is reasonably accurate when used in the measurement of sequestered

plasma volume (100) . The average plasma volume deficit in the patients with aspiration pneumonitis, 450ml., is greater than the mean increase in extravascular lung water, 150 ml., measured by double isotope dilution technique by Gump and co-workers (104,105) in acutely ill patients with shock or sepsis. But it lies well within the known range of plasma volume losses into the lung in pulmonary oedema from other causes (106). Assuming a predicted plasma volume of 4.5% of body weight in the normal adult (101) the maximal plasma volume deficit of 1100 ml. found in the 75 kg. patient #2,J.R., is approximately the same as the maximal decrease of 35% of the plasma volume found experimentally by Awe (53).

Moreover, our patients have shown an increasing fall in blood pressure as plasma volume deficit increased, thus lending clinical support to Awe's hypothesis, based purely on experimental data, that hypovolaemia plays an important role in the hypotension seen in aspiration pneumonitis. When the plasma volume deficit was less than 500 ml., hypotension sometimes occured immediately following aspiration. The cause of this is uncertain. Colebatch and Halmagyi (72) suggested a reflex mechanism ; but circulatory depression produced by the severe hypoxia we have noted is probably an adequate explanation (103). With larger plasma volume deficits we have observed a greater and more sustained progressive fall in blood pressure. As plasma volume replacement restores the blood pressure it may be assumed that hypovolaemia is the cause of this hypotension.

It is important,however, to note the average magnitude and range of plasma volume deficits found.The average plasma losses were moderate - 450 ml. It follows that patients with aspiration pneumonitis should be closely monitored for evidence of hypovolaemia. Further, when hypovolaemia is suggested by fall in blood pressure, rising haematocrit , low central venous pressure, or decreasing measured plasma volumes, the deficit should be replaced by moderate volumes of colloid .Large volumes are not required; we have seen that larger volumes of non-colloid fluid will restore the circulation in these patients , but often only at the expense of increasing pulmonary oedema. Aspiration pneumonitis, like the pneumonitis seen in septicaemia demands colloid rather than crystalloid intravenous fluids, in the smallest volumes necessary to correct hypovolaemia. Pontoppidan (107) has pointed out that in acute respiratory insufficiency the usual formulae for water and salt replacement do not apply. Aspiration pneumonitis illustrates this point ; fluid must be administered by "budget" rather than by "formula". As Moore states,(101) a budget is a forecast plan that must be changed according to varying needs and circumstances; it is not a precise formula to be pursued with a compulsive desire to avoid change.

Cardiac indices measured in the uncomplicated patient with aspiration pneumonitis were normal, and increased following fluid administration.In the clinical case report available in which cardiac index was measured (35)the cardiac index was initially low, but rose to well above normal following fluid administration.

Experimental studies have shown the same trend (53,55).Our patients were already receiving intravenous fluids at the time of initial determination of cardiac output and this possibly increased cardiac output slightly. Since the normal response to hypoxaemia is an increased cardiac output, even a normal cardiac output in these conditions may be considered low (83).

The important question is whether patients with aspiration pneumonitis respond to hypoxaemia with increased or decreased cardiac output.Several factors complicate assessment of this response in our patients. These include hypovolaemia , ventilatory therapy , previous operation and concurrent sepsis. Hypovolaemia decreases cardiac output , hence the increased cardiac output observed following restoration of blood volume .

The circulatory effect of ventilatory therapy has been studied by several workers (108 - 114). The results of these studies show that three factors may be important - mean alveolar pressure,oxygen consumption and P_{CO_2} . Mean alveolar pressure is increased during positive pressure breathing; it causes a decrease in venous return to the heart, decreasing the cardiac output.This decrease is sustained in patients with emphysema, but in non-emphysematous patients, on positive pressure ventilation even with peak airway pressures over 100 cm.of water, venous return and cardiac output are restored promptly by a compensatory rise in peripheral venous pressure (114). When Expiratory Positive Pressure in excess of 5 cm. of water is employed a sustained decrease in cardiac output may be recorded (110).

Normally only one to three percent of the total oxygen consumption is required for the oxygen cost of breathing. In patients with acute respiratory insufficiency the oxygen cost of breathing may cause an increase of total oxygen consumption of as much as 36% (115). When the energy expenditure for this work is managed completely by respirator , the oxygen required is decreased considerably. The demand for muscle blood flow is reduced and cardiac output is thus decfeased .Grenvik (112) found a 23% increase in cardiac index upon changing from controlled to spontaneous ventilation in postoperative thoracic surgical patients. The simultaneous increase in oxygen consumption was 8%.

Prys-Roberts (113) found an inverse linear relationship between P_{CO_2} and cardiac output during artificial ventilation of anaesthetized patients; and proposed that arterial P_{CO_2} was the prime regulator of the circulatory response to artificial ventilation. But Geffin and associates (107) repeated the study in conscious patients, and while confirming Prys-Robert's finding in some patients found that the overall circulatory response to variations in P_{CO_2} was unpredictable.

Our patients with aspiration pneumonitis were all on Intermittent Positive Pressure Ventilation (IPPV) when the cardiac output was measured .They were all dyspnoeic when breathing spontaneously ; and all but one (#2) were hypocapneic.

The circulatory response to operative trauma has been studied by Clowes (116), Billig (117) and Eisele (118).Eisele found no change in cardiac index after extensive abdominal operations,except in those patients who seemed to be hypovolaemic ; and rigid fluid restriction may also have accounted for the decreased postoperative cardiac indices observed by Clowes. But in Billig's study cardiac index rose on the first postoperative day.He suggested that this reflected the increased circulatory requirements for the inflammatory reaction which accompanies wound healing.Four patients in whom we measured cardiac index at the onset of aspiration pneumonitis were in the postoperative state.

High cardiac outputs have often been noted in severe stress states, in hepatic cirrhosis and in septic shock (4,6,12,119 - 122); the cardiac index may be low when there is significant hypovolaemia in the course of septic shock.The mechanism of high cardiac output, low total peripheral resistance, low arteriovenous oxygen content difference, and lacticacidaemia in these states may be systemic arteriovenous shunting; but Duff and MacLean (123) have suggested that in severe sepsis the demand for high outputs may be caused by failure of oxygen utilization due to cellular damage rather than to systemic shunting. Hermreck and Thal (124) observed a 50% increase in cardiac index following creation of a septic leg in dogs; and suggested that a vasodilator, possibly an endogenous pyrogen released from bacterial host - tissue interaction, is released from the septic region ,and causes vasodilatation in

distant vascular beds rather than perfusion of non-nutrient (shunt) vessels. We have confirmed this pattern of high cardiac output and low peripheral resistance in patients with sepsis. One of our patients with aspiration pneumonitis (#9) had peritoneal sepsis, and another (#11) had cirrhosis and portal hypertension. In both the cardiac indices were elevated , probably because of these factors.

Among the patients with aspiration pneumonitis evidence of heart failure was present only in those patients with known pre-existing coronary heart disease, and in two patients who were over-transfused. In the other patients we have interpreted a normal cardiac index and a CVP less than 10 cm. of water as indicating absence of cardiac failure.These may not represent an entirely adequate estimate of cardiac mechanical performance for left ventricular end-diastolic pressure may be increased in the absence of a decreased cardiac output .However, pulmonary wedge pressures or left atrial pressures were not available, and the CVP appeared to be a reliable guide. In over 200 patients in shock, following open heart surgery, and elderly patients at surgery, MacLean observed pulmonary oedema only once when the CVP was less than 15 cm. of water (125).

On this basis we conclude that heart failure does not occur in aspiration pneumonitis except in patients with established heart disease or following overtransfusion. Myocardial ischaemia may occur and was evidenced in our patients by ECG changes, but

the main pulmonary changes were not due to heart failure. It follows that digitalis and rigorous fluid restriction are required only in the treatment of those patients with heart disease or overtransfusion who go into heart failure.Ventilatory compensation for hypoxaemia is far more efficient than circulatory compensation (76) ; therefore oxygen administration and ventilatory support are more logical steps in the treatment of the patient without heart failure.Moreover, in this situation digitalis is of doubtful value (126), and prophylactic digitalisation in comparable clinical situations carries significant complications, especially the effects of digitalis intoxication (127).

Pontoppidan (107) has recommended the use of diuretic therapy in acute respiratory insufficiency, on the grounds that many patients receiving artificial ventilation have a reduced ability to handle free water. Skillman (128) observed a greater improvement in hypoproteinaemia, serum osmotic pressure and A-a difference in patients treated with albumin and Ethacrynic acid than in those treated with albumin alone. Furosemide was used in patients Nos. 11 and 15 with clinical improvement following diuresis.There may be, then, a special place for diuretic therapy in the treatment of aspiration pneumonitis.

The finding in patient # 14 of pulmonary hypertension associated with hypoxaemia and its reversal upon full saturation supports our hypothesis on the mechanism of pulmonary hypertension in aspiration pneumonitis. Either left heart failure

or increased pulmonary vascular resistance must have been present; the prompt response to oxygen suggests the latter mechanism. This patient had mild acidosis which may have augmented the pulmonary vasoconstrictor response to hypoxaemia.Clowes (129) has recently found right ventricular systolic pressures greater than 35 mm.Hg. in six of ten patients with severe peritonitis.There was no evidence of left heart failure.He attributed the pulmonary hypertension to mechanical interference with the free passage of blood through the pulmonary capillaries which were plugged with erythrocytes ;but noted also that fibrinopeptides associated with disseminated intravascular coagulation might play a role. Pulmonary hypertension in these patients caused right heart failure with an elevated CVP. Digitalis was given and was beneficial.If hypoxaemia is the primary cause of pulmonary hypertension in aspiration pneumonitis, oxygen is the treatment of choice, though digitalis may be indicated if right heart failure ensues.

Respiratory Gas Exchange. The pattern of respiratory gas exchange found supports the experimental and clinical data available and is compatible with the maldistribution of ventilation known to occur in pulmonary oedema. In any clinical situation hypoxaemia may be due to one or more of four causes- hypoventilation, impaired diffusion of oxygen, a low ventilation perfusion ratio or physiological shunting (76,95,97,103,130). In our patients the low or normal P_{CO_2} throughout most of their course excludes hypoventilation; and since alveolar P_{O_2} was much greater than 90 mm.Hg. impaired diffusion of oxygen is unlikely to have been

significant. The A-a difference following 100% oxygen breathing was used to differentiate low ventilation perfusion ratio and physiological shunting.Under these conditions hypoxaemia due to under-ventilation of perfused alveoli is usually abolished (95, 103). The finding of marked widening of the A-a difference after 100% oxygen breathing in our patients with aspiration pneumonitis therefore indicates a marked increase in physiological shunting.

Physiological shunting in the lung represents the sum of anatomical shunting through arteriovenous anastomoses, pleural, bronchial and Thebesian veins, (normally 1 - 2%), and capillary shunting due to perfusion of totally unventilated alveoli. Alveoli may be unventilated because of atelectasis or due to small airway obstruction by oedema fluid and foam. The finding that the shunt effect was reversed by forcible inflation using positive pressure ventilation which presumably re-opens closed alveoli suggests that atelectasis is the major mechanism. In this regard the observation by Said (131) of marked increase of A-a difference in experimentally produced pulmonary oedema, and that by Cook (132) of a 78% fall in pulmonary compliance and a mean physiological shunt of 45% in pulmonary oedema, both well within the range of changes expected in atelectasis , are highly significant.

Expiratory Positive Pressure was required to reduce the A-a difference in 3 patients. Ashbaugh (133), Pontoppidan (107) and

others (109) have pointed out that whereas in the normal lung with low surface tension little pressure is required to maintain a normal alveolar radius at end-expiration, when surfactant is lost and surface tension rises the alveolar wall will collapse at end-expiration unless positive pressure is maintained on the airway throughout expiration.In this respect our autopsy finding of hyaline membranes lining the alveoli of patients with aspiration pneumonitis supports the experimental finding of decreased alveolar surfactant by Greenfield (55) and correlates with the clinical course of the patients .It may be too, that pulmonary arteriolar vasoconstriction and decreased pulmonary blood flow due to sustained hypoxia caused decreased synthesis of alveolar surfactant thus contributing to alveolar instability. Increased capillary permeability with alveolar oedema would also produce change in surface forces and shunting , even though surfactant synthesis per se was normal (132). We have employed albumin and Furosemide as advocated by Skillman (128) to promote diuresis and decrease the A-a difference.

An increased A-a difference may be caused by factors other than increased venous admixture. These include increased cardiac output, decreased arteriovenous oxygen content difference and decreased oxygen consumption .The most important of these is cardiac output. Hedley-Whyte (114) has shown that the right to left shunt correlates well with the cardiac index. He attributed this to redistribution of blood flow due to lower resistance in the shunt capillaries than in those associated with ventilated

alveoli; and to decreased arterial oxygen saturation due to an inadequate perfusion time when the cardiac index is high. The A-a differences in our patients were far greater than could be explained by changes in cardiac indices which were at most slightly increased. Occasionally administration of 100% oxygen for determination of the A-a difference itself produces redistribution of the pulmonary blood flow resulting in an increased A-a difference (107).

We have not attempted to calculate the magnitude of the right to left shunt in our patients. The shunt fraction decreases as arteriovenous oxygen content difference increases. The latter was not available and as we could not predict its magnitude in patients with aspiration pneumonitis or in those with shock or sepsis, the shunt calculation was omitted. Moreover, the calculation itself adds little to our understanding of the patho - physiology of aspiration pneumonitis.

Hypoxaemia was associated with hyperventilation and respiratory alkalosis or tissue hypoxia and metabolic acidosis, except in patients with pre-existing chronic obstructive lung disease, who had respiratory acidosis. The mild elevation of P_{CO_2} in patients without chronic obstructive lung disease reflected an increased airway resistance and decreased compliance resulting in total alveolar hypoventilation.

The marked decrease in dynamic compliance in aspiration pneumonitis is in agreement with previous experimental findings (32,42,43) and with the clinical findings in pneumonitis due to inhalation burns. The decrease is slightly larger than that found by Garzon (44) who measured static compliance in patients with inhalation burns. This reflects the effect of concomitant increase in airway resistance in decreasing dynamic compliance, as the latter measures both airway resistance and elastic forces. Increased airway resistance may have been promoted by the hypocapnia which predominated in the course of most patients; but we have no clinical evidence pointing specifically to this.

Pulmonary Infection. Our results confirm the experimental evidence indicating that early aspiration pneumonitis is non-infective. The uniform development of subsequent infection results from the impairment of the normal mechanisms of pulmonary clearance of infectious agents. Physical removal of these agents by cough and expectoration and the mucociliary "escalator" is depressed in the elderly or critically ill patient. Of the antimicrobial mechanisms, Green(134) has pointed out that hypoxia suppresses the activity of the antibacterial alveolar macrophage. This combination permits the accumulation and multiplication of bacteria. The frequency of Pseudomonas as the sole organism or dominant organism in mixed pulmonary infections following aspiration, may be explained by its unique ability to multiply in the respiratory tract (135).

Abscess formation may result from the specific activity of Staphylococci, or from progressive accumulation of infected secretions in patients with impaired ability to clear them. Prolonged transport times along the tracheobronchial tree have been noted in patients with chronic obstructive lung disease, but increased coughing normally compensates for this (134). When cough is depressed in these patients decompensation of mechanisms of physical clearance follows. This may explain the fact that both patients who had gross abscess formation in the lung had chronic obstructive lung disease. Prolonged administration of steroids may also have favoured the development of abscess .Intravenous steroid treatment is of definite benefit in suppressing the inflammatory response in aspiration pneumonitis (38,57,136);but its value is probably limited to the first few hours ,and at most the first 24 hours after aspiration of highly acid secretions (137). Continued administration beyond 24 to 48 hours probably facilitates the spread of pulmonary infection by suppressing the cellular and humoral antimicrobial mechanisms of pulmonary clearance.

Prophylactic antibiotics did not prevent subsequent development of infection and may have permitted the emergence of strains resistant to antibiotics used. Antibiotics should not therefore be given prophylactically. Infection may be present immediately following aspiration of faecal vomitus, or in patients who have been hospitalised for some time prior to aspiration. In these groups antibiotics may be used therapeutically from the onset of pneumonitis. Two well defined groups of pulmonary infections

emerged subsequently; the Gram-positive ,dominated by Staphylococcus , and the Gram-negative infections.Gram-stain of the sputum should be done daily during aspiration pneumonitis. The appropriate antibiotic can then be selected readily when infection appears in the sputum.

Mortality. Aspiration pneumonitis in the critically ill patient carries a high mortality; 40% of patients died as a direct consequence of aspiration pneumonitis. This mortality was related to the age of the patient, the pH of aspirated gastric contents, the duration of severe hypoxaemia , the presence of concurrent sepsis and the effects of ensuing pulmonary infection. The mean age of survivors was half that of those who died. Elderly patients show diminished cardiopulmonary reserve (103) and can mobilise pulmonary oedema and diurese less readily. Gastric aspirate of pH less than 1.75 carried a much higher mortality than aspirate of greater pH value.This is probably related to the direct chemical effect of acid upon the lungs.

The mean duration of severe hypoxaemia in deaths was twice as long as that in survivors. The rapidity of resolution of early aspiration pneumonitis was closely related to diuresis. Thus rapid resolution in patients nos. 6,10,13 and 16 was related to prompt diuresis;while the more protracted course in patients nos. 1,2,5,11 and 15 may have been related to more limited diuresis. In a controlled study of patients with atelectasis ,

pneumonia and pulmonary oedema, Skillman (128) has recently drawn a strong correlation between the diuretic response to albumin and Ethacrynic acid and improvement in A-a difference.

We have noted cerebral, hepatic and pulmonary effects of hypoxia. The cerebral effects of hypoxia are well known (76,129). Two patients with aspiration pneumonitis showed clinical signs of severe cerebral effects persisting after resuscitation. The effects of hypotension may be superimposed upon those of hypoxia. Adams (138) has studied the effects of systemic hypotension on the brain.He noted that precipitate reduction of systemic blood pressure (such as may occur immediately following aspiration) produces localised infarcts limited to the "watershed" zones between regional areas of arterial supply in the cerebrum and cerebellum; whereas moderate but sustained hypotension (such as may result from hypovolaemia in untreated aspiration pneumonitis) is associated with diffuse loss of neurons in the cerebrum and cerebellum.

The liver is normally protected from the effects of hypoxia by its large oxygen reserves (77); but almost no circulatory compensation is available to the liver in severe hypoxaemia (76). In this situation , in patients with pre-existing liver disease, fatal liver cell necrosis has been observed (139) preceding cerebral and myocardial effects. This progression of liver cell disease may be associated with renal failure in the seriously ill patient probably due to concurrent low renal blood flow. We

have observed this sequence of events in two patients.The effects of pulmonary ischaemia have been alluded to above.

Concurrent wound and peritoneal sepsis was present nearly twice as often in those dying as in survivors. The mechanism by which concurrent sepsis affects the mortality is uncertain. It may be related to the circulatory requirements for oxygen transport which it imposes on the already hypoxaemic patient. The mechanism of these circulatory changes is discussed above. It is interesting that a high mortality was also seen in our patients with severe sepsis who were studied separately .

CHAPTER 8. SUMMARY and CONCLUSIONS.

Cardiopulmonary studies in 18 patients with chemical pneumonitis due to gastric aspiration or smoke inhalation have been correlated with serial routine laboratory, X-ray and pathologic findings. Results have been compared with those of cardiopulmonary studies done on 13 patients with shock or severe sepsis.

i. The pH of aspirated gastric contents affects the course and prognosis of aspiration pneumonitis. Mortality was 100% in patients whose gastric aspirate was of pH less than 1.75; and much lower in patients whose aspirate was of greater pH. pH of aspirated gastric contents should be determined as a guide to prognosis and treatment of aspiration pneumonitis.

ii. The pattern of hypoxaemia and widened alveolar-arterial oxygen difference in aspiration pneumonitis suggests maldistribution of ventilation compatible with pulmonary oedema. Increased airway resistance and reduced compliance were observed.This response indicates the presence of atelectasis , such as occurs when alveolar cells are damaged and surfactant is deficient ;and correlates with the finding of hyaline membranes lining the alveolar walls. IPPV was generally beneficial in decreasing pulmonary

oedema and improving the A-a difference.However, in some patients with protracted pneumonitis Expiratory Positive Pressure was required.

iii. Measured plasma volume deficits were moderate, averaging about 500 ml.,and correlated with the degree of hypotension observed. Plasma volume losses above 500 ml. should be replaced cautiously with moderate volumes of colloid rather than larger quantities of crystalloid solutions.

iv. There was no evidence of heart failure in patients with aspiration pneumonitis except in patients with known pre-existing heart disease or overtransfusion. Rigorous fluid restriction and digitalis are therefore unwarranted except in the latter patients; but combined treatment with albumin and potent diuretics may facilitate elimination of pulmonary oedema fluid.

v. The pneumonitis was non-infective at the outset except when aspiration was of faecal vomitus, and in those patients who had been hospitalised for some time prior to aspiration. Prophylactic antibiotics did not prevent development of pulmonary infection , and sometimes permitted evolution of bacterial strains resistant to the antibiotics used. Antibiotics are

not indicated routinely in aspiration pneumonitis . When infection appears antibiotics may readily be chosen on the basis of the specific organism indicated by Gram-stain of the sputum.

vi. Pulmonary hypertension was observed in one patient who was markedly hypoxaemic; it was abolished following oxygen administration.Hypoxaemia may be the dominant cause of pulmonary hypertension in aspiration pneumonitis.

vii. The mortality as a direct consequence of aspiration pneumonitis was 40%; while that of the patients with shock or sepsis was 69.2% . The main factors influencing mortality were the age of the patient, the pH of aspirated gastric contents, the duration of severe hypoxaemia, the presence of concurrent sepsis and the effects of ensuing pulmonary infection.

APPENDIX

ILLUSTRATIVE CASE REPORTS

Patients with Aspiration Pneumonitis.

Pt.#12,M.H. This 82 year old woman was admitted to the M.G.H. on the 6th.March,1970, with a fracture of her right femoral neck,suffered three weeks previously. Her vital signs were normal; pulse rate 82/min.,blood pressure 148/65 mm.Hg.,respiratory rate 23 per min. Her chest X-ray was within normal limits. She was taken to the operating room where hip-pinning was done without complication .Two days postoperatively, she had a cerebrovascular accident,and following a generalised seizure, she vomited and aspirated gastric contents of pH 1.3 Over the next 8 hours, her respiratory rate increased progressively, and she became cyanotic. Examination of the chest revealed coarse crepitations and harsh breath sounds in the right lung base. Her blood pressure fell to 90/40 mm.Hg.,pulse rate rose to 128 per min., her skin was cool and moist and she became oliguric. Blood gases showed severe hypoxaemia and respiratory alkalosis; and blood volume and haematocrit determinations indicated moderate plasma volume depletion. Her perfusion improved after a rapid load of 500 ml.normal saline in 30 minutes,and maintenance fluids thereafter. Over the next two days, after diuresis, her respiratory status improved; but deteriorated again with the development of bronchopneumonia.She died a week later, primarily due to her neurological disease,but with concomitant bronchopneumonia.

Comment. Elderly patient aspirated due to a cerebrovascular accident with convulsions during the period of gastrointestinal ileus following a hip-pinning operation. She developed aspiration pneumonitis and subsequently bronchopneumonia,and eventually died.

Pt. #13.L.T. This was a 13 year old school girl who had her first epileptic seizure and became comatose shortly after recess for lunch at school on the 10th.March,1970. On initial examination, her pulse rate was 120 per min., blood pressure 110/70 mm.Hg., respirations 23 per min., and her chest was clear.During examination she vomited and aspirated gastric contents of pH 2.7,and became cyanotic and dyspnoeic with pulse rate 50 per min., blood pressure 150/70 mm.Hg., respirations 52 per min. Chest X-ray revealed diffuse pulmonary oedema and carotid angiography diffuse cerebral oedema. Despite resuscitation with airway, oxygen, positive pressure ventilation and steroids, blood gases during angiography indicated metabolic acidosis due to severe hypoxia and widened alveolar-arterial oxygen gradient.Overnight she had a prompt diuresis and improved progressively until discharge.

Comment. Moderately severe aspiration pneumonitis arising during post-ictal coma, with prompt resolution on treatment.

Pt. #9.F.B. This 45 year old paranoid schizophrenic man aspirated gastric contents of pH 2.0 in the perianaesthetic period following cholecystectomy and external drainage of a pancreatic

abscess. He developed mild aspiration pneumonitis with hypoxaemia, increased A-a oxygen difference and respiratory alkalosis which resolved promptly with oxygen and intermittent positive pressure ventilation. He showed no significant plasma volume changes and no evidence of heart failure.

Comment. Mild aspiration pneumonitis following peri - anaesthetic aspiration with prompt resolution on treatment.

Pt. #11. C.F. This 51 year old cirrhotic with portal hypertension was admitted with bleeding oesophageal varices on the 21st. February,1970. Bleeding stopped promptly following transfusion, intravenous pitressin and introduction of the Sengstaken-Blakemore tube. She remained stable over the next two days and then bled again. During reintroduction of the Sengstaken -Blakemore tube she vomited and aspirated gastric contents. Bleeding stopped spontaneously over the next 12 hours, but she developed severe aspiration pneumonitis.Her hypoxaemia and widened alveolar-arterial oxygen difference increased following overtransfusion with non-colloid fluids,and despite tracheostomy and somewhat inefficient positive pressure ventilation until the 28th.March. Over the weekend, with the establishment of efficient positive pressure ventilation,fluid restriction and diuretics ,her pulmonary function improved markedly.However, during the period of severe hypoxia,her liver function worsened as indicated by progressive increase in bilirubin and serum enzyme concentrations; and subsequently her renal function deteriorated .Four days later, she

started to bleed again, and in view of her renal and hepatic failure, it was decided to discontinue respiratory support. She died 30 minutes later.

Comment. Aspiration pneumonitis following aspiration during Sengstaken-Blakemore intubation in a patient with bleeding oesophageal varices. Pulmonary insufficiency was aggravated by overtransfusion, and improved by fluid restriction, IPPB, PEPP and oxygen; but the severe hypoxic period left organ damage and residual pulmonary insufficiency demanding respiratory support, and when this was withdrawn, she died.

Pt. #2. J.R. A 74 year old alcoholic man with previously undiagnosed emphysema was admitted to the M.G.H. on the 6th. October, 1969, in respiratory distress following vomiting and aspiration of gastric contents during alcoholic stupor. His pulse rate was 120 per min., blood pressure 95/45 mm.Hg., and respirations 40 per minute. He was treated with oxygen, IPPB, animophylline and antibiotics. One hour following admission, his blood pressure had fallen to 70/30 mm.Hg. Rapid intravenous fluid therapy was started, and 12 hours later his pulse and blood pressure were almost normal, though he was still dyspnoeic. Two days later he became worse due to development of Staphylococcal pneumonia, and tracheostomy and bronchoscopy were performed with improvement. Thereafter he had repeated relapses due to repeated aspiration, as indicated by hypoxaemia, widened alveolar-arterial oxygen difference

and respiratory acidosis . On each occasion he improved rapidly following administration of oxygen, antibiotics, steroids and continuous positive pressure ventilation. Eventually he developed septic shock secondary to pneumonia and lung abscess formation, and died despite attempts at resuscitation.

Comment. Recurrent aspiration pneumonitis in an elderly alcoholic patient with chronic lung disease responding rapidly to treatment, but culminating in shock and death due to Staphylococcal infection and lung abscess formation.

Pt.# 5.C.M. This 86 year old woman was admitted to the M.G.H. following aspiration of faeculent vomitus of pH 1.7 in the course of septic shock secondary to a urinary infection. Her pulse rate was 110 per min., blood pressure 80/50 mm.Hg., respiratory rate 32 per min., and temperature 102 ^{o}F. A diverticular abscess was diagnosed in error and she was subjected to laparotomy .Post - operatively she had progressively increasing respiratory insufficiency ,radiological changes compatible with aspiration pneumonitis, and severe hypoxaemia, widened alveolar -arterial oxygen difference, respiratory alkalosis and a low cardiac index. Despite treatment with blood, non-colloid fluid, steroids, antibiotics and positive pressure ventilation with oxygen, she deteriorated and died 18 hours later.

Comment. Aspiration pneumonitis in the course of Proteus mirabilis septicaemia secondary to urinary infection, proved a rapidly fatal combination despite vigorous treatment in this elderly patient.

Pt.#4. M.S. This 21 year old secretary was trapped in a burning building and was admitted on the morning of the 26 th. October, 1969.On examination, she was semistuporous,and had burns of the oral and oropharyngeal mucous membranes.Her chest was clear, and vital signs were normal. That evening ,she developed increasing respiratory difficulty.Blood gases showed hypoxaemia, widened alveolar-arterial oxygen difference, and metabolic acidosis. Tracheostomy was done,and positive pressure treatment with oxygen instituted.Improvement was slow, but progressive ,over the next five days,when positive pressure ventilation was discontinued and the tracheostomy removed.

Comment. Smoke inhalation pneumonitis in a young woman, demonstrating a pattern of respiratory gas exchange similar to that in acid aspiration pneumonitis.

Patients with Shock or Sepsis

Pt. #5a.J.M. This 68 year old man was admitted to the M.G.H. on the 6th. of November, 1969 complaining of pain in the left costovertebral angle and left groin of two weeks' duration, vomiting and malaise for one week and haematemesis on the day of admission .On examination he was emaciated and showed moderate dehydration , but his vital signs were normal.There was tenderness in the left loin and mild peripheral oedema. The IVP showed a normal right kidney and a left staghorn calculus with minimal left-sided renal function. Following volume replacement he improved initially but then developed marked swelling of the left buttock and thigh and became hypotensive.He remained afebrile .Iliofemoral thrombosis with possible pulmonary embolism was suspected but 12 hours later, needling of the left flank yielded frank pus and the diagnosis of left perinephric abscess with septic shock was made. At operation,the large perinephric abscess extending into the buttock was drained. Postoperatively, his blood pressure returned to normal levels, but he developed progressive pulmonary insufficiency,with bilateral infiltration and atelectasis on chest X-ray, decreased compliance and widened A-a difference.Three days later he had a severe bout of upper gastrointestinal bleeding and required large volumes of blood and fluids to maintain his blood pressure. On this therapy his pulmonary function deteriorated further.IPPV with oxygen was started and produced some improvement initially, but he reaccumulated pus in his retroperitoneal space and developed

septic shock again on November 18th. Over the next two days he had further gastrointestinal bleeding, oliguria and progressive azotaemia, and continued deterioration of pulmonary function despite ventilatory therapy culminated in death on November 20th.

Comment. Elderly man with an undiagnosed left perinephric abscess leading to E. coli septicaemia and shock. Pulmonary function deteriorated probably due to increased pulmonary capillary permeability and to the increased fluid administration necessitated by recurrent gastrointestinal bleeding and an expanded vascular capacitance. Death was due to overwhelming sepsis, renal and pulmonary failure.

Pt. #10a. J.Z. This was a 67 year old man with a pancreatic abscess admitted to the M.G.H. on January 10th, 1970. His pulse was 110 per min., respirations 20 per min., blood pressure 140/70 mm.Hg., temperature 100 ^{o}F , and a tender mass was palpable in the epigastrium. Chest X-ray showed some basal atelectasis and a small left pleural effusion. Forty-eight hours after external drainage of the abscess he showed evidence of progressive respiratory failure , his P_{CO_2} rising to 55 mm.Hg., on January 12th. A naso-tracheal tube was inserted and IPPV instituted. Following rapid blood and plasma administration necessitated by gradual decline of his haematocrit and plasma protein levels, he developed congestive heart failure. His ECG showed widespread ST and T -wave changes suggestive of myocardial ischaemia , His heart failure responded to treatment, and with continued ventilatory therapy he

improved rapidly. On January 15th he was extubated and two days later he was discharged to the surgical ward where his recovery thereafter was uneventful.

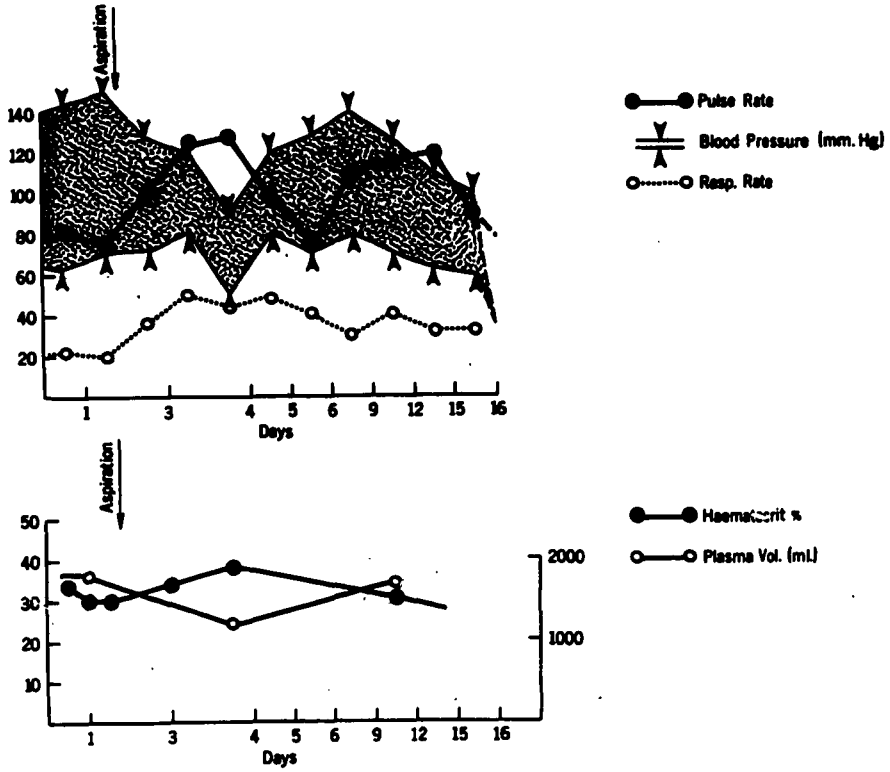
Comment. Elderly man with a pancreatic abscess leading to "High Output Respiratory Failure" (11) following operative drainage. His recovery with ventilatory support was further complicated by transient congestive heart failure following blood transfusion.

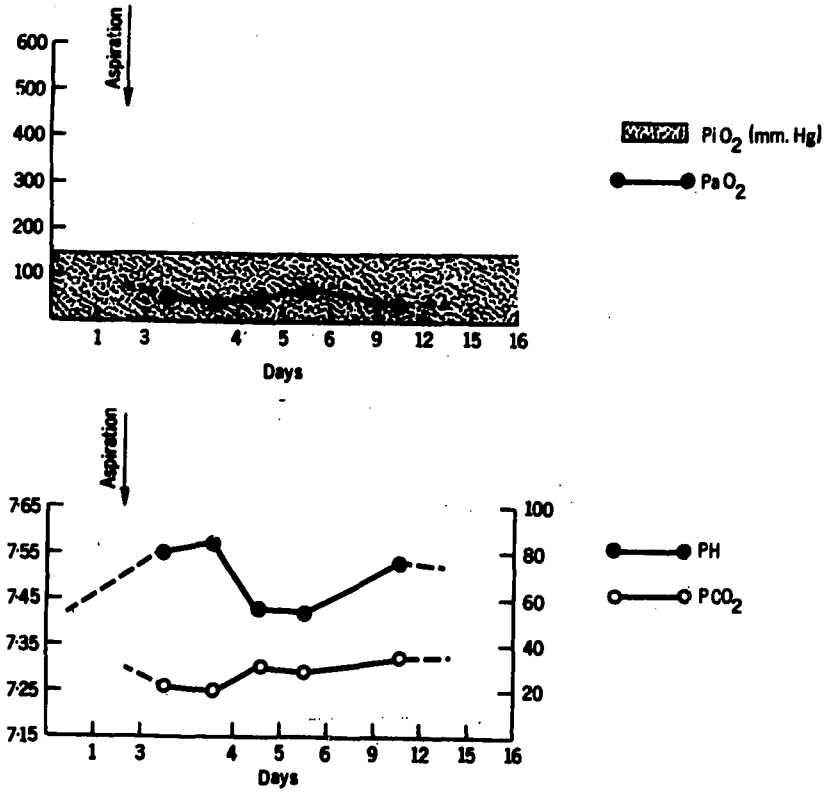
Pt. # 2a. N.M. This 65 year old man with a ruptured abdominal aortic aneurysm was transferred to the M.G.H. on January 21st.,1970, in haemorrhagic shock. His blood pressure was 50/? mm.Hg. He was taken to the operating room where repair was done. For 3 hours peroperatively he was anuric but towards the end of the operation he began producing urine again; and on admission to the Intensive Care Unit his vital signs were stable. Six hours later he became hypotensive because of retroperitoneal and intra- abdominal bleeding associated with a "massive transfusion" coagulopathy . During retransfusion he became severely hypoxaemic with a markedly widened A-a difference. He was slightly dyspneic and was hyperventilating but his chest was clear. Chest X-ray showed pulmonary vascular congestion and linear atelectasis .The heart sounds were barely audible. He had suffered a myocardial infarction one year previously and his clinical status and ECG now suggested re-infarction .Blood pressure and tissue perfusion could not be maintained despite transfusion, digitalisation, vasopressors and

pharmacologic doses of steroids and pulmonary function deteriorated further despite ventilatory support. Within 12 hours he became anuric and he died six hours later.At autopsy there was no evidence of recent myocardial infarction, but the ventricular wall showed aneurysmal dilatation at the site of the previous infarct.

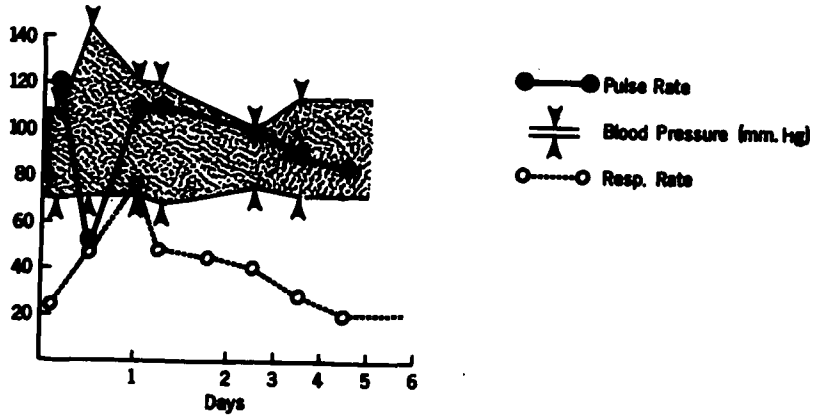
Comment. Elderly man with a generalised atherosclerosis and a ruptured abdominal aortic aneurysm who bled post-operatively .He dcveloped interstitial pulmonary oedema and miliary atelectasis with severe hypoxaemia and widened A-a difference as a result of ventricular aneurysm formation and heart failure. He developed shock refractory to all therapy because of continued hypovolaemia and myocardial failure; and died within 18 hours of operation.

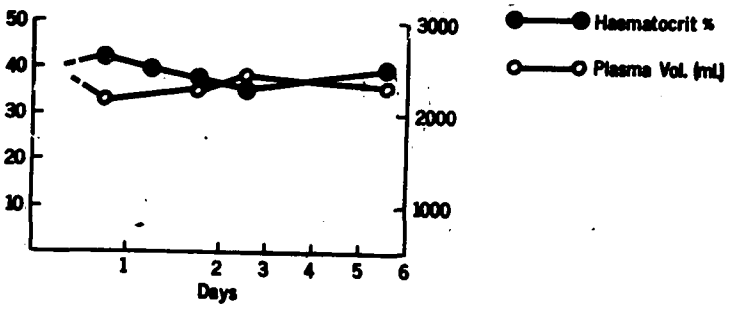
Pt. # 12, M.H.

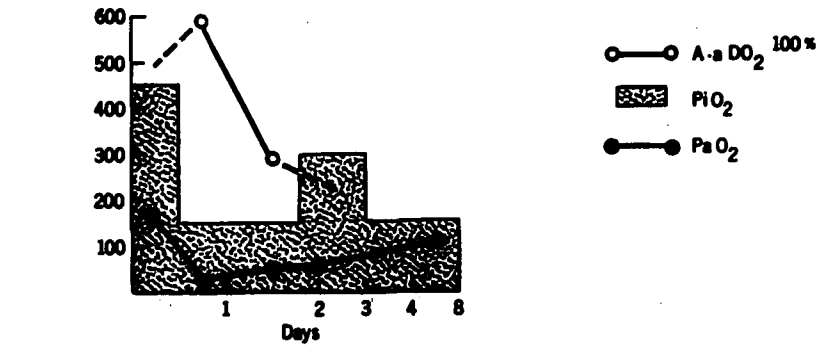

Aspiration
140
120
100
80
60
40
20
1 3 4 5 6 9 12 15 16
Days
Pulse Rate
Blood Pressure (mm. Hg)
Resp. Rate
Aspiration
50
40
30
20
10
2000
1000
1 3 4 5 6 9 12 15 16
Days
Haematocrit %
Plasma Vol. (ml.)


Aspiration
600
500
400
300
200
100
1 3 4 5 6 9 12 15 16
Days
PIO_2 (mm. Hg)
PaO_2
Aspiration
7·65
7·55
7·45
7·35
7·25
7·15
100
80
60
40
20
1 3 4 5 6 9 12 15 16
Days
PH
PCO_2

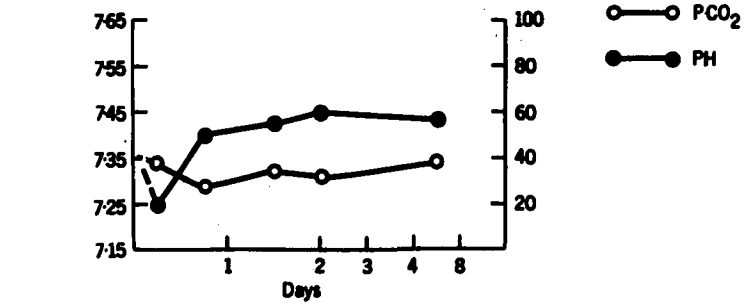
Pt. # 13, L.T.



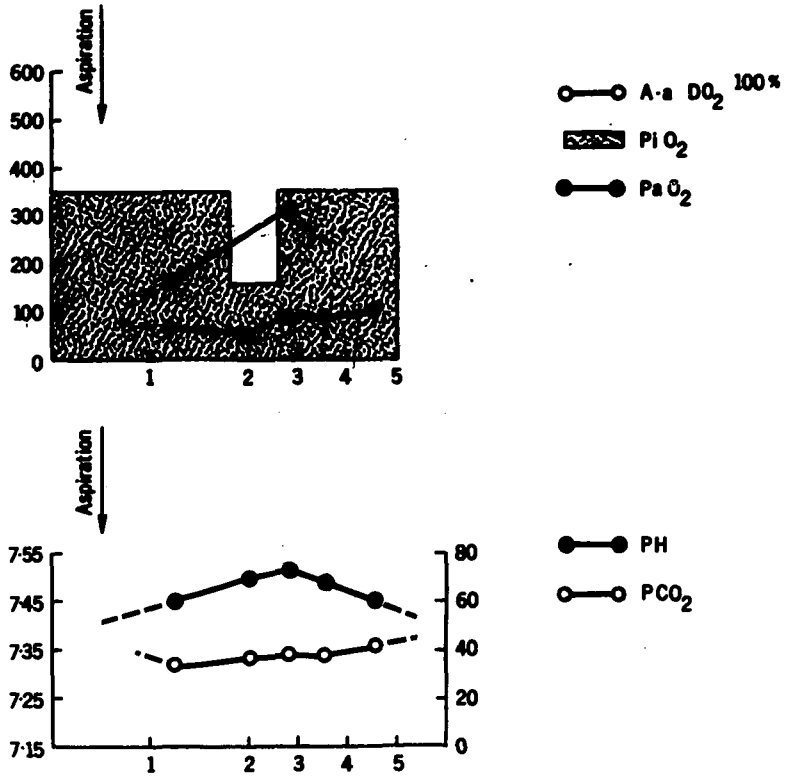




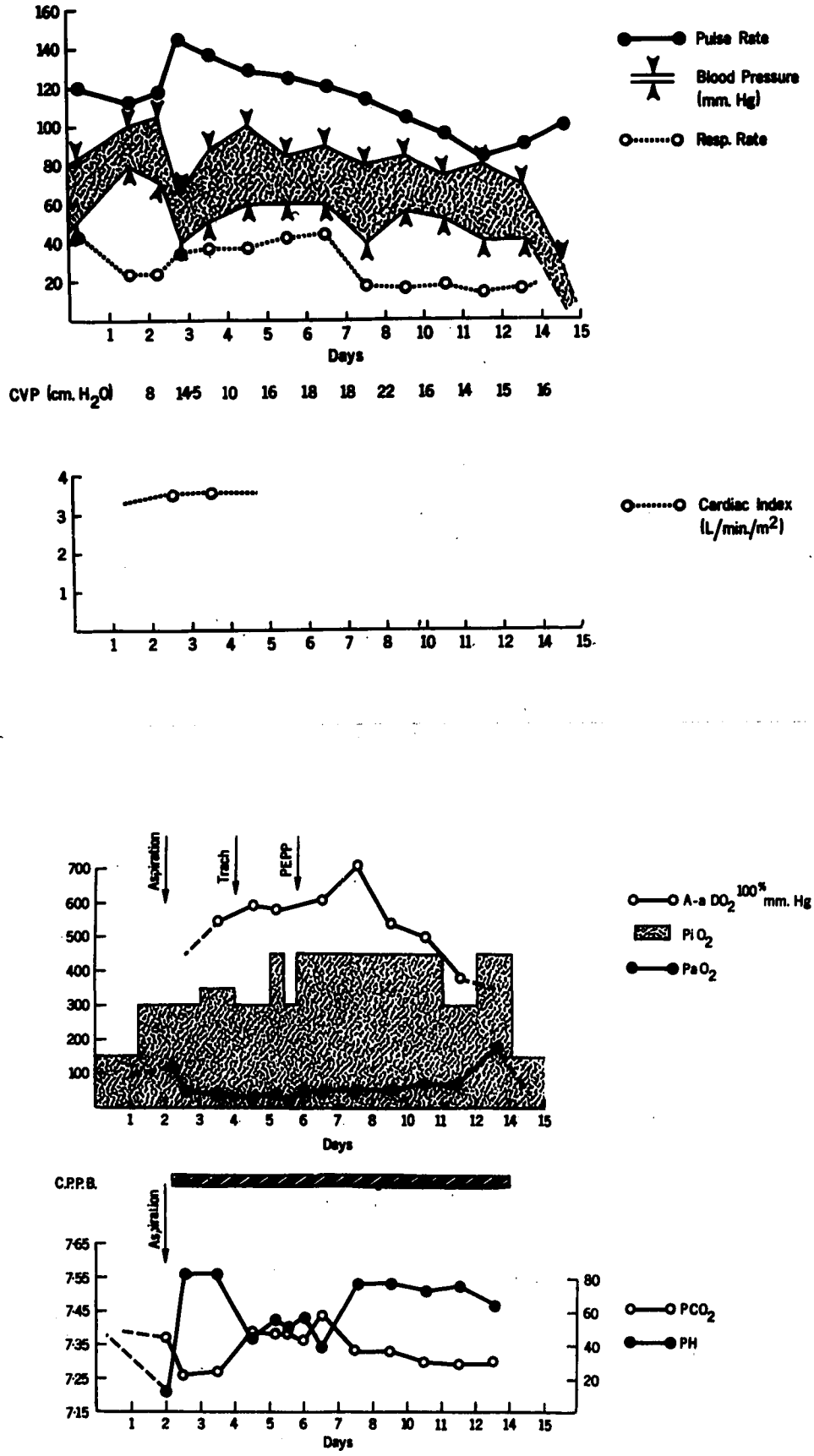
CPPB IPPB



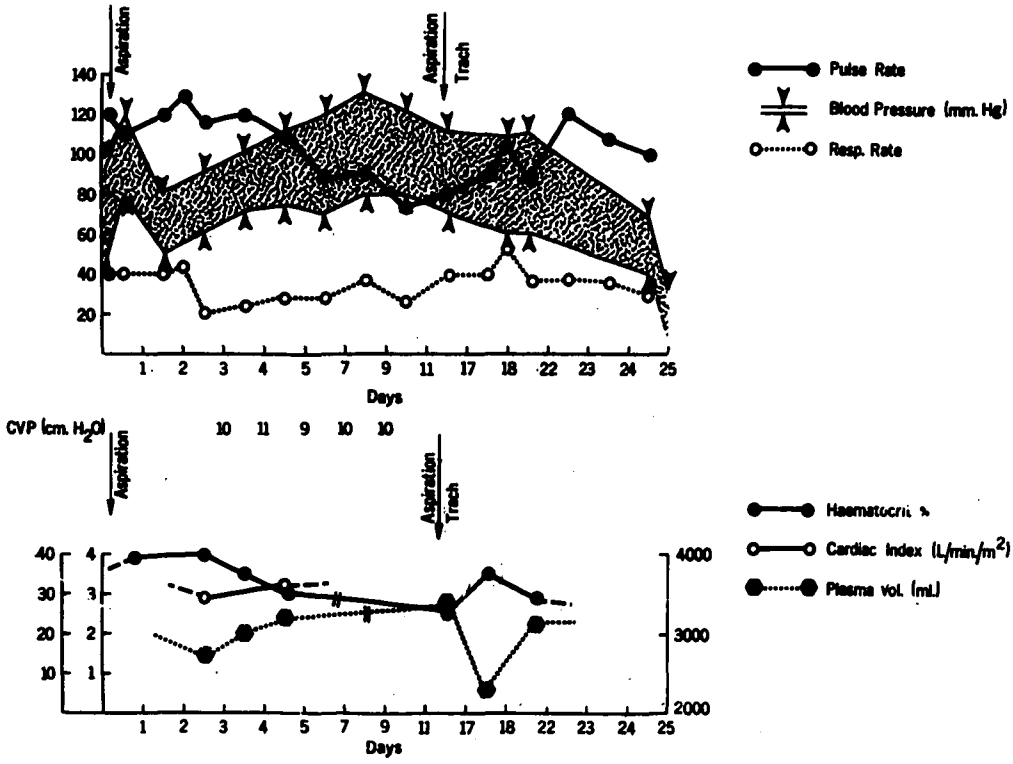
Pt. #9, F.B.

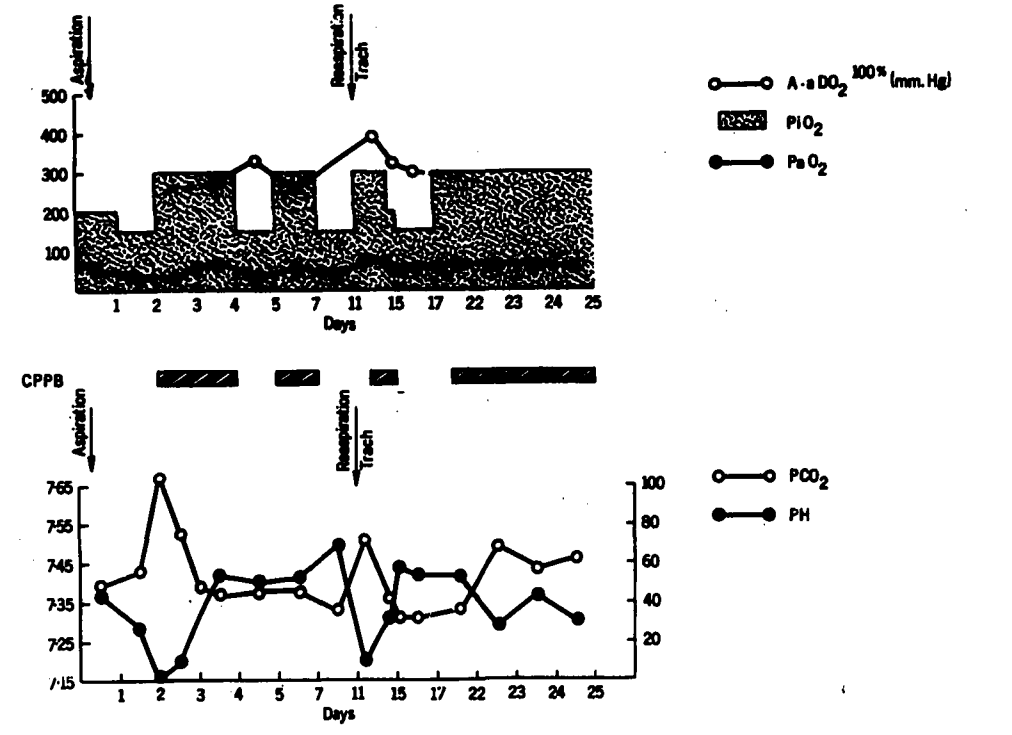

Aspiration
600
500
400
300
200
100
0
1
2
3
4
5
A-a DO_2 100%
PiO_2
PaO_2
Aspiration
7·55
7·45
7·35
7·25
7·15
80
60
40
20
0
PH
PCO_2

Pt. # 11, C.F.

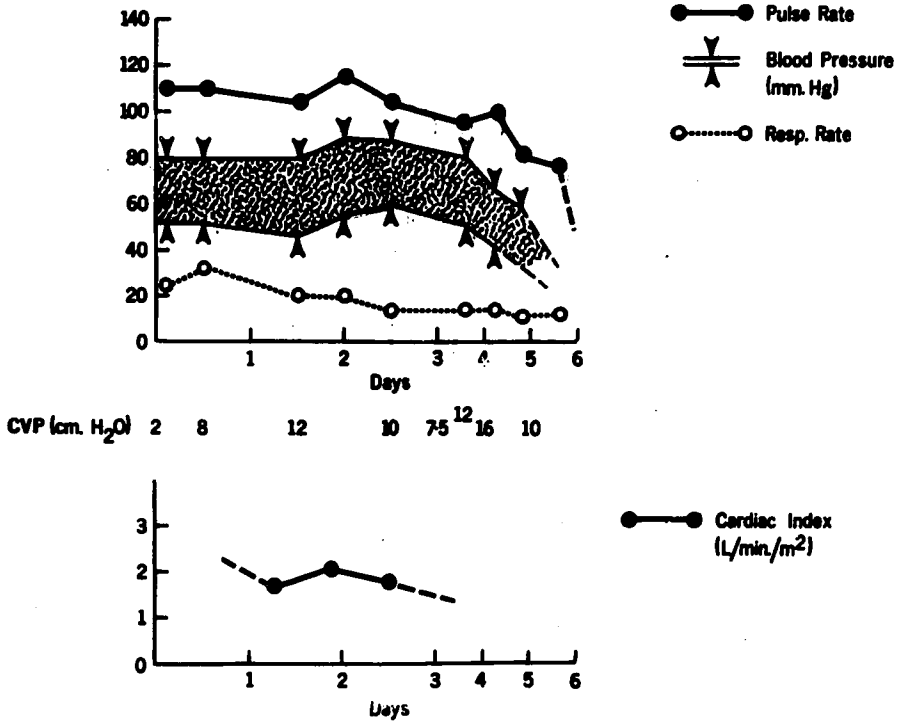

160
140
120
100
80
60
40
20
1 2 3 4 5 6 7 8 10 11 12 14 15
Days
Pulse Rate
Blood Pressure (mm. Hg)
Resp. Rate
CVP (cm. H2O) 8 14-5 10 16 18 18 22 16 14 15 16
4
3
2
1
1 2 3 4 5 6 7 8 10 11 12 14 15
Cardiac Index (L/min./m2)
Aspiration
Trach
PEPP
700
600
500
400
300
200
100
1 2 3 4 5 6 7 8 10 11 12 14 15
Days
A-a DO2 100% mm. Hg
PiO2
PaO2
C.P.P.B.
Aspiration
7·65
7·55
7·45
7·35
7·25
7·15
80
60
40
20
1 2 3 4 5 6 7 8 10 11 12 14 15
Days
PCO2
PH

Pt. # 2, J.R.


Aspiration
Aspiration
Trach
Pulse Rate
Blood Pressure (mm. Hg)
Resp. Rate
Days
CVP (cm. H_2O)
10 11 9 10 10
Aspiration
Aspiration
Trach
Haematocrit %
Cardiac Index ($L/min/m^2$)
Plasma vol. (mL)
Days


Aspiration
Resuscitation
Trach
A-a DO_2 100% (mm. Hg)
PIO_2
PaO_2
Days
CPPB
Aspiration
Resuscitation
Trach
PCO_2
PH
Days

Pt. # 5, C.M.


140
120
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40
20
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2
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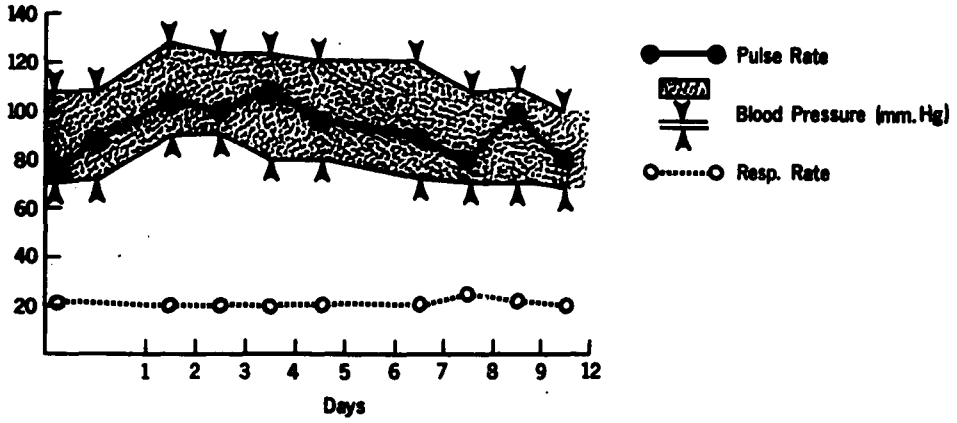
4
5
6
Days
Pulse Rate
Blood Pressure (mm. Hg)
Resp. Rate
CVP (cm. H_2O) 2 8 12 10 7-5 12 16 10
3
2
1
0
1
2
3
4
5
6
Days
Cardiac Index ($L/min./m^2$)

Pt. # 4, M.S.


140
120
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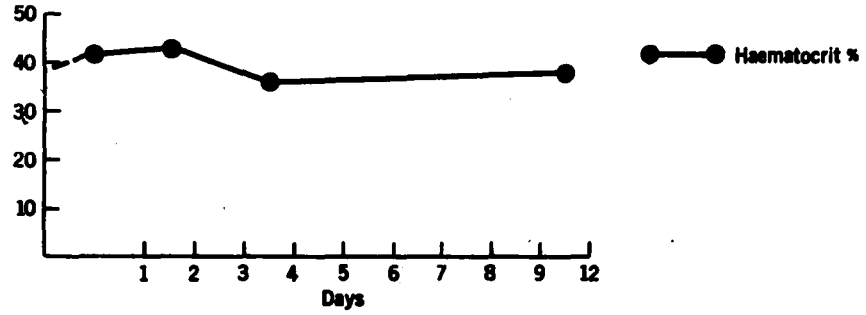
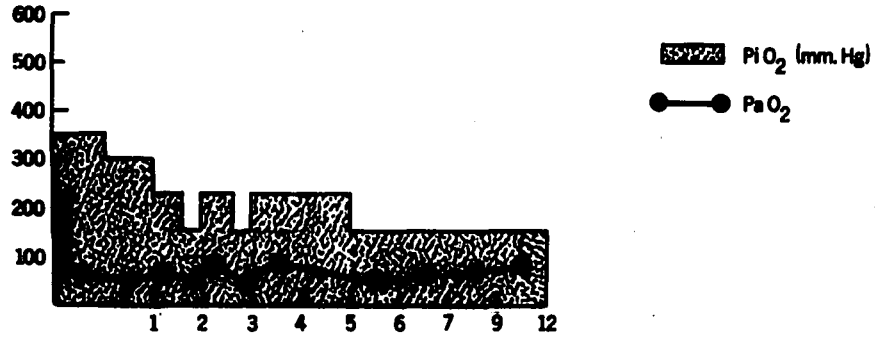
1 2 3 4 5 6 7 8 9 12
Days
Pulse Rate
Blood Pressure (mm. Hg)
Resp. Rate


50
40
30
20
10
1 2 3 4 5 6 7 8 9 12
Days
Haematocrit %


600
500
400
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100
1 2 3 4 5 6 7 9 12
PIO2 (mm. Hg)
PaO2

C.P.P.B.

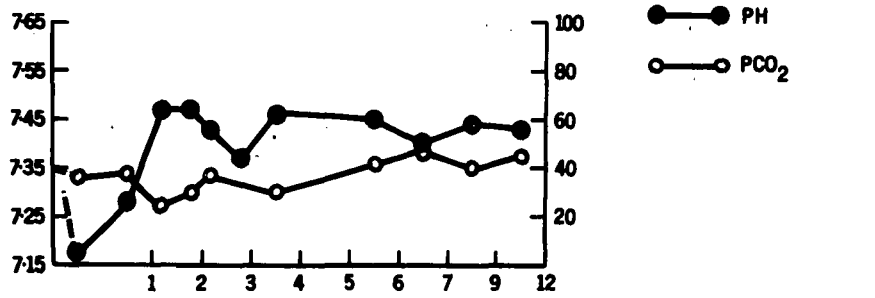
7·65
7·55
7·45
7·35
7·25
7·15
100
80
60
40
20
1 2 3 4 5 6 7 9 12
PH
PCO2

TABLE 1

CAUSES OF ASPIRATION

Coma or Semi-Coma	7 Patients
Gastrointestinal Ileus	6 Patients
Perianaesthetic Accident	4 Patients

TABLE II

SIGNIFICANCE OF pH OF ASPIRATE

pH 1.2 - 1.75				pH 1.75 - 2.4				pH ≤ 2.4			
Pt.	pH Range 1.2 - 1.75	Lowest p^{O}_{2}	Fate	Pt.	pH Range 1.75 - 2.4	Lowest p^{O}_{2}	Fate	Pt.	pH Range 2.4	Lowest p^{O}_{2}	Fate
5	1.7	49	D	3	2.2	54	D	13	2.7	30	S
10	1.45	58	D	6	1.9	49	S	8	2.4	59	D
12	1.3	42	D	18	2.0	48	S				
17	1.7	40	D	9	2.0	65	S				

Mean Lowest p^{O}_{2} = 52 Mean Lowest p^{O}_{2} = 54

Mortality = 100% Mortality = 25%

D = Died S = Survived

TABLE III

EFFECT OF PLASMA VOLUME DEFICIT ON BLOOD PRESSURE

A. Plasma Volume Deficit Less Than 500 ml.

Pt.	Normal Mean Blood Pressure mm.Hg.	Post Aspiration Changes in Blood Pressure mm.Hg.	
		Immediate	After 12 Hours
8	93	- 26	- 10
13	83	+ 14	+ 4
16	94	+ 3	- 10
18	74	- 7	+ 3

TABLE III

B. Plasma Volume Deficit 500 to 1000 ml.

Pt.	Normal Mean Blood Pressure mm.Hg.	Post Aspiration Changes in Blood Pressure mm.Hg.	
		Immediate	After 12 Hours
3	100	-	- 20
4	80	+ 4	+ 4
9	96	+ 8	+ 10
12	92	+ 11	- 28
14	113	- 13	- 23
17	97	- 30	- 33

C. Plasma Volume Deficit Greater Than 1000 ml.

Pt.	Normal Mean Blood Pressure mm.Hg.	Post Aspiration Changes in Blood Pressure mm.Hg.	
		Immediate	After 12 Hours
2	95	- 33	- 45

TABLE IV

HAEMODYNAMIC CHANGES IN ASPIRATION PNEUMONITIS

Pt.	CVP (cm. water)		Cardiac Index ($L/M^2/min.$) and Peripheral Resistance ($dynes/sec/cm^5$)		EKG
1	Initial	At 24 hours	Initial	At 24 hours	
1.	1.3	11	2.81 (2331)	3.35 (1013)	Progressively worsening ischaemia
2.	10	9	2.91 (1170)	3.17 (1300)	Premature atrial and ventricular beats
5.	3	8	1.73 (1988)	1.80 (1650)	Non-specific ST-T wave changes
9.	3.5	3.0	3.85 (1127)	4.16 (1096)	Sinus tachycardia
11.	9.5	15.0	-	3.50 (1042)	Progressively worsening ischaemia

TABLE V

PULMONARY HYPERTENSION Pt.~~#~~ 14 G.M.

	O_2 Saturation %	R. Ventricular Pressure (Systolic) mm. Hg.
Before Oxygenation	76	59
After Oxygenation	98	34

TABLE VI - SURVEY OF HAEMODYNAMIC AND ARTERIAL BLOOD GAS CHANGES

Patient	Lowest P_{O_2} mm. Hg.	Highest $AaDO_2^{1.0}$	pH	Highest P_{CO_2} mm. Hg.	Cardiac Index $L/m^2/min.$	CVP cm.H_2O	
						Initial	Later
1. H.L.	45	522	7.16 resp.	78 #	2.81	1.3	11
2. J.R.	32	400	7.14 resp.	105 #	2.91	10	9
3. H.M.	54	-	7.45 resp.	66 #	-	13	10
4. M.S.	47	-	7.17 met.	47	-	-	-
5. C.M.	49	640	7.53 resp.	29.5	1.73	3	8
6. D.B.	49	189 (24 hr.)	7.24 met.	46	-	6	7
7. C.P.	47	-	7.54 resp.	46	-	2	7
8. J.D.	59	-	7.46 resp.	48 #	-	2.5	- 1
9. F.B.	65*	313	7.50 resp.	43	3.85	3.5	3.0
10. F.D.	58*	547	7.47 resp.	52	-	-	-
11. C.F.	25	685	7.56 resp.	52	3.50	9.5	15
12. M.H.	42	-	7.57 resp.	34	-	-	-
13. L.T.	30	580	7.25 met.	38	-	-	-
14. G.M.	49	370	7.285 resp.	53.5 #	-	16	13
15. M.O'C.	40	619	7.29 met.	47	-	3	9
16. E.H.	68	-	7.40 met.	33.5	-	-	-
17. N.McG.	37	375	7.30 met.	38.6	-	9	9
18. C.W.	48	-	7.41 met.	55.7 #	-	-	-

* After treatment established : initial sample unsatisfactory.

Chronic obstructive lung disease.

met. = metabolic

resp. = respiratory

TABLE VII

CHANGES IN LUNG-THORACIC COMPLIANCE

Patient	Compliances (L/cm. H_2O)	
	Lowest	Clinical Improvement
7.	0.025	-
10.	0.018	0.026
11.	0.017	0.022
13.	0.014	0.047
15.	0.023	-
17.	0.022	0.030

TABLE VIII

CHANGES IN LUNG-THORACIC COMPLIANCE AND A -a GRADIENT

Pt. #11		Pt. #15	
Compliance L/cm. H_2O	1.0 A -a DO_2 mm.Hg.	Compliance L/cm. H_2O	1.0 A -a DO_2 mm.Hg.
0.023	572	0.032	468
0.020	595	0.044	594
0.0177	685	0.023	619
0.022	500	0.024	564
0.018	343	0.023	604

TABLE IX

PULMONARY INFECTION AFTER ASPIRATION

Patient	Initial Sputum Culture	Subsequent Sputum Culture	Antibiotics from Onset
1	Negative	Staphylococcus	Yes
2	-	Staphylococcus	Yes
3	Escherichia sp.	Escherichia sp.	Yes
4	Negative	Negative	None
5	-	Proteus sp.	Yes
6	-	Staphylococcus	Yes
7	-	Pseudomonas sp.	Yes
8	Negative	Mixed	Yes
9	Negative	Negative	Yes
10	Mixed	Mixed	Yes
11	Negative	Staphylococcus	None
12	Staphylococcus	Mixed	Yes
13	Negative	Negative	Yes
14	Negative	Escherichia sp.	Yes
15	Negative	Staphylococcus	Yes
16	Negative	D. pneumoniae	None
17	Escherichia sp.	Pseudomonas sp.	Yes
18	D. pneumoniae	A. aerogenes P. intermedius	Yes

TABLE X - MORTALITY

SURVIVORS

Patient	Age	Concurrent Sepsis	Duration of Hypoxaemia (Days)	Lowest P_{O_2} (mm.Hg.)
1. H.L.	64	Peritoneal Infection	15	45
4. M.S.	21	None	9	47
6. D.B.	15	None	8	49
9. F.B.	45	Peritoneal Infection	3	65
13. L.T.	13	None	2	30
14. G.M.	58	Peritoneal Infection	3	49
16. E.H.	22	None	1	40
18. C.W.	29	None	4	48

DEATHS

Patient	Age	Concurrent Sepsis	Duration of Hypoxaemia (Days)	Lowest P_{O_2} (mm.Hg.)
2. J.R.	74	Pulmonary Infection Septic Shock	20	32
3. H.M.	69	Wound Infection	16	54
5. C.M.	86	Urinary Infection Septic Shock	6	49
7. C.P.	77	Wound Infection	14	47
8. J.D.	71	Pulmonary Infection Septic Shock	15	47
10. F.D.	62	Peritoneal Wound Infection	3	58
11. C.F.	51	Pulmonary Infection Bacteraemia	12	25
12. M.H.	82	None	12	42
15. M.O'C	73	Peritoneal Infection Septic Shock	12	40
17. N.McG.	61	Peritoneal Wound Infection	10	37

TABLE XI

MORTALITY

	Survivors	Deaths
Mean Age	34.6	70.6
Mean Duration of Hypoxaemia (Days)	5.6	12
Mean Lowest P_{O_2} (mm.Hg.)	46.6	43.1
Pulmonary Sepsis	5/8 (62.5%)	10/10 (100%)
Concurrent Sepsis elsewhere	3/8 (37.5%)	6/10 (60%)

Overall Mortality = 10/18 (55.6%)

Mortality as a Direct Consequence of Aspiration = 7/18 (40%)

TABLE XII - HAEMODYNAMIC CHANGES IN SHOCK AND SEPSIS

SEPSIS OR SEPTIC SHOCK

Patient	Initial			Intermediate			Subsequent			Fate
	C.I.	TPR	CVP	C.I.	TPR	CVP	C.I.	TPR	CVP	
5. J.M.	3.05	754	9	3.15	1620	2	3.07	1029	5	Died
6. W.H.	3.30 (Isuprel)	760	8	3.36 (Dibenzyline)	687	9	3.24	712	6	Died
7. C.M.	1.73	1988	15	2.03 (Isuprel)	1650	10	1.8	1871	12	Died
8. M.E.	2.41	1927	9.5	3.14	1046	6.5	2.81	1374	13	Died
9. R.M.	3.73	1041	11	4.34	1043	11.5	-	-	12	Died
10. J.Z.	4.4	671	8	3.31	932	9.5	-	-	-	Survived
11. A.M.	1.16	2043	3	1.73	2095	11	2.65	1405	9	Survived
12. A.R.	2.9	1118	8.5	-	-	12	-	-	12	Died
13. M.B.	-	-	16	3.34 (Isuprel)	1280	9	-	-	-	Survived

HAEMORRHAGIC SHOCK

Patient	Initial			Intermediate			Subsequent			Fate
	C.I.	TPR	CVP	C.I.	TPR	CVP	C.I.	TPR	CVP	
1. H.M.	1.22	2834	7				1.84	2538	10	Died
2. N.M.	3.51	1160	11				1.84	1745	9	Died
3. J.G.	2.49	906	8.5				1.44	2005	7	Died
4. E.J.	2.02	2335	15				3.3	1500	10	Survived

C.I. = Cardiac Index ($L/m^2/min.$)
TPR = Total Peripheral, Resistance ($dynes/sec/cm^5$)
CVP = Central Venous Pressure

TABLE XIII

BLOOD GAS AND PH CHANGES IN SHOCK AND SEPSIS

Patient	Lowest P_{O_2} mm. Hg.	Highest A-a DO_2 1.0 mm. Hg.	Highest P_{CO_2} mm. Hg.	pH
1. H.M.	52	-	65 #	7.35 metabolic
2. N.M.	36	624	43	7.25 metabolic
3. J.G.	50	642	46	7.39 metabolic
4. E.J.	40	403	40	7.30 metabolic
5. J.M.	41	446	42	7.64 respiratory
6. W.H.	44	431	56 #	7.75 respiratory
7. C.M.	49	620	29.5	7.39 metabolic
8. M.E.	60	411	53	7.57 respiratory
9. R.M.	44	372	35	7.45 respiratory
10. J.Z.	40	491	55	7.33 metabolic
11. A.M.	56	300	36	7.35 metabolic
12.A.R.	52	378	36	7.36 metabolic
13. M.B.	56	243	37	7.49 respiratory

Chronic Obstructive Lung Disease

Figure 1. Low power Photomicrograph of the lung in aspiration pneumonia illustrating dense leucocyte infiltrate in the alveolar exudate,and vegetable particles with a giant cell reaction.

Figure 2. Higher magnification (x10) showing Hyaline membrane deposition on the alveolar wall.

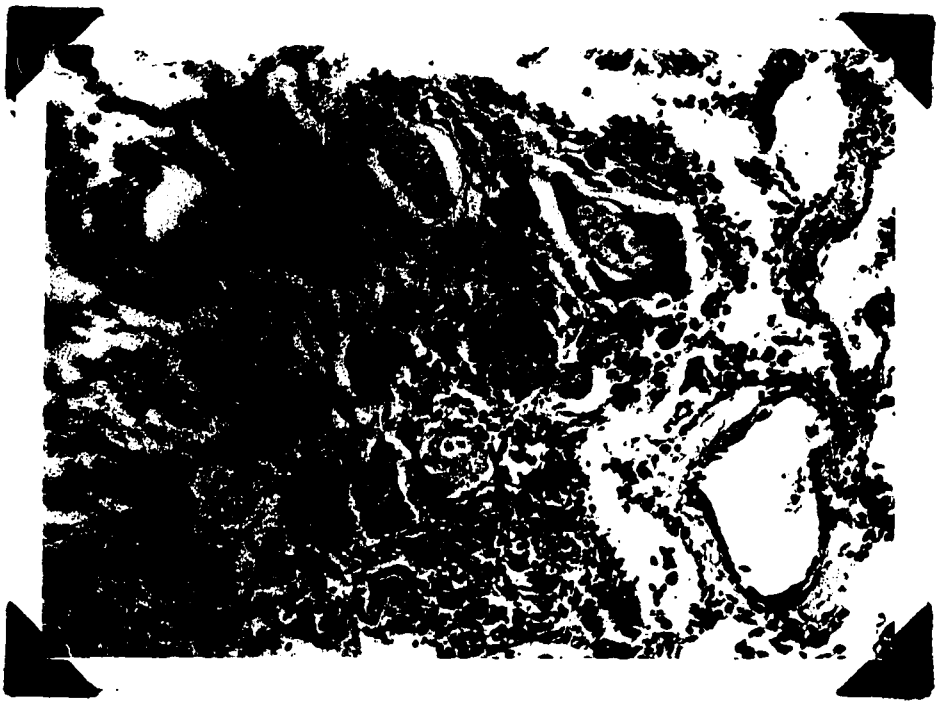

Figure 1. Low power Photomicrograph of the lung in aspiration pneumonia illustrating dense leucocyte infiltrate in the alveolar exudate, and vegetable particles with a giant cell reaction.

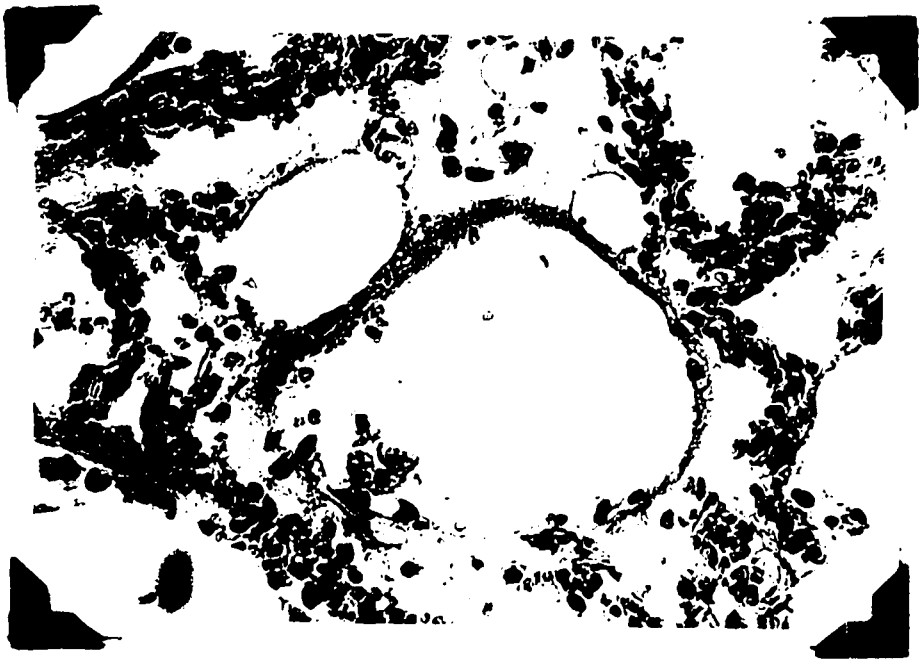

Figure 2. Higher magnification (x10) showing hyaline membrane deposition on the alveolar wall.

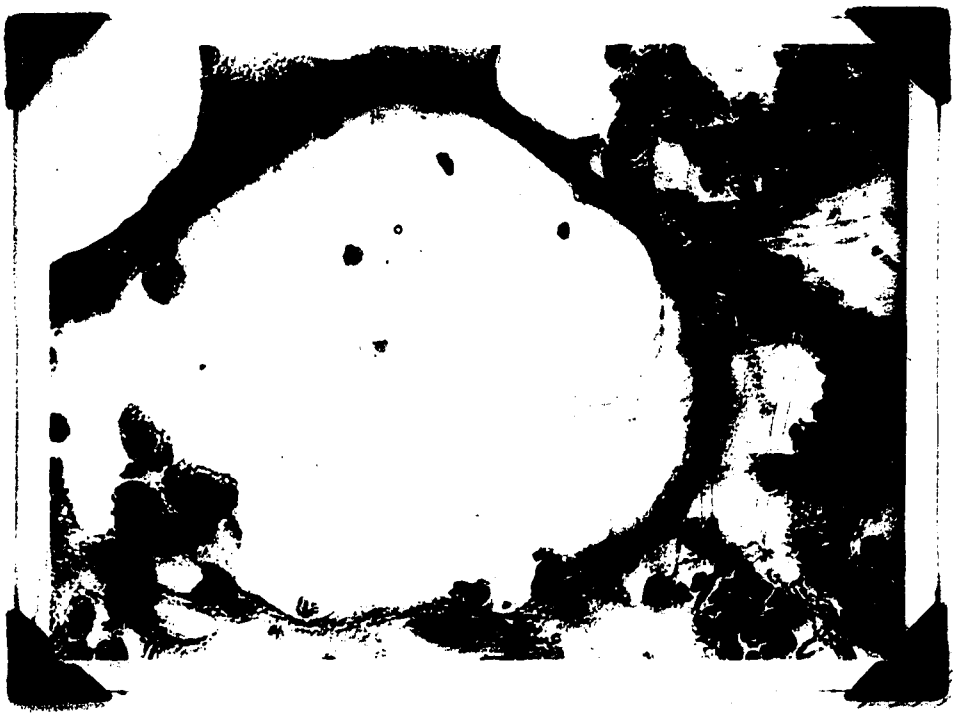

Figure 3. Still higher magnification (x42) showing Hyaline membrane formation more clearly.

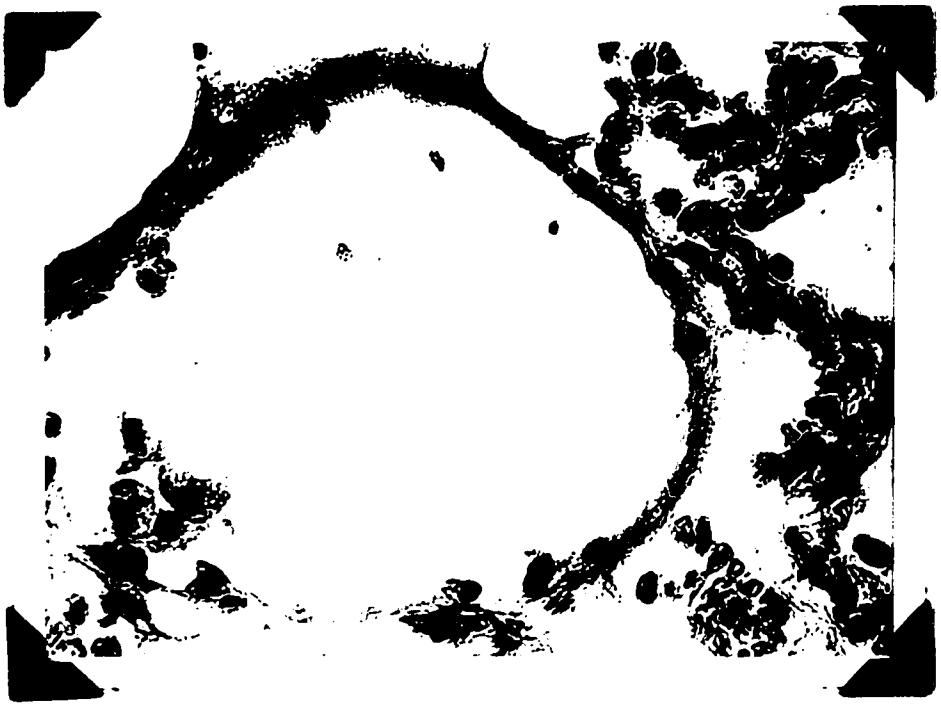

Figure 3. Still higher magnification (x42) showing Hyaline membrane formation more clearly.

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