MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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ACUTE RESPIRATORY DISTRESS IN ADULTS:

THE SYNDROMES OF ACUTE ALVEOLAR INJURY

The acute onset of marked dyspnea, tachypnea, cyanosis and bilateral alveolar infiltrates radiographically is a common clinical disorder. This syndrome is most often due to acute pulmonary edema secondary to left ventricular failure and the principles of therapy are well known to clinicians. There are a group of disorders, however, in which the initial presentation of the patient may mimic cardiogenic pulmonary edema, but which may not respond to the usual modes of therapy. These disorders are the result of diffuse alveolar injury produced by inhaled, aspirated, or ingested toxic substances or result from similar lung injury produced by endogenous mechanisms. In both cardiogenic pulmonary edema and the syndromes of diffuse alveolar injury, the patient's major symptoms and physiologic alterations are the result of fluid in the alveolar spaces. This review will examine the features which these disorders have in common, discuss pathogenetic mechanisms, and develop a program of therapy based on the rather limited information available at the present time.

Case #1: [redacted]

This 56-year-old woman was admitted with a 4-hour history of marked shortness of breath. She had noted increasing exertional dyspnea for approximately one month prior to admission. Physical examination revealed a markedly dyspneic, cyanotic, obese woman. BP 130/90, P 110, RR 32. The jugular venous pressure was elevated. There were diffuse crepitant rales at both lung bases. The heart was enlarged; a loud S_3 gallop was present. A radiograph of the chest showed cardiomegaly, venous congestion, and a diffuse alveolar infiltrate in both lower lung fields. Arterial blood gases, breathing room air, were: pH 7.10, pCO_2 39, pO_2 32, 43% saturation of hemoglobin.

Treatment with digitalis, diuretics, IPPB, oxygen, and morphine was begun. Eight hours later a repeat arterial blood sample, while the patient breathed 40% oxygen via a face mask, showed: pH 7.40, pCO_2 39, pO_2 78, 95% saturation. A chest radiograph 24 hours after admission showed clearing of most of the alveolar infiltrates. Serial ECG's and enzymes did not reveal evidence of myocardial infarction, and she was discharged on the 5th hospital day.

Diagnoses: 1. Acute pulmonary edema secondary to left ventricular failure. 2. Metabolic acidosis, secondary to severe hypoxia.

The factors involved in the fluid equilibrium of the lung may be visualized with a diagramatic representation of the Starling hypothesis, as shown in Figure 1 (1). Hydrostatic pressure in the capillaries is the principal force tending to drive water out of the intravascular space; also augmenting movement of water out of the capillary are the colloid osmotic pressure of the interstitial fluid, the negative pressure of the interstitial space, and the surface tension of adjacent alveoli which produces a negative pressure on the walls of the alveolus. Forces which tend to retain water in the capillary are the colloid osmotic pressure of blood and positive pressure, when present, in the alveolus. Lymphatics are probably not present in the walls of alveoli but originate in the vicinity of alveolar ducts and extravascular fluid may be removed via this route.

The pulmonary capillaries are normally freely permeable to water and low molecular weight solutes but only slowly permeable to larger molecules (2, 3). Although the lungs have a very high blood flow with respect to the mass of tissue, the flow of lymph from the lungs is only a few mls per hour (4), and alveolar spaces do not normally contain fluid. These observations indicate that there is virtually no net transfer of water out of the pulmonary capillaries. Further, water or saline instilled into the lungs is rapidly absorbed suggesting that either an unbalanced osmotic gradient for fluid reabsorption exists or that the interstitial fluid volume is so small that the addition of small volumes of fluid lowers its osmotic pressure, providing a gradient for absorption into the capillaries (5).

The relationship of the two dominant forces, hydrostatic pressure and plasma colloid osmotic pressure, has been defined in experimental animals and these observations correlate well with measurements performed in humans. Other factors remaining unchanged, pulmonary edema begins to accumulate when hydrostatic pressure in the capillaries (usually measured clinically as a "wedge pressure") exceeds 24 mm Hg (6, 7). If plasma colloid osmotic pressure is reduced by one-half by removing protein, edema develops when hydrostatic pressure is approximately 12 mm Hg (6). Hydrostatic pulmonary edema may be more occult than that demonstrated by Case 1. The pulmonary edema which occasionally accompanies massive CNS injury may be due to a sudden increase in peripheral vascular resistance followed by an increase in left ventricular end-diastolic and left atrial pressure (8). Hypoxemia may contribute to the formation of pulmonary edema; it has been suggested that one mechanism may be through a depression of myocardial contractility with subsequent elevation of end-diastolic

pressure (9). Pulmonary venous constriction is another mechanism which has been postulated to cause pulmonary edema on a hydrostatic basis (10). This phenomenon is difficult to measure physiologically since, by the wedged catheter technique, the small pulmonary arterioles, capillaries, and veins form a single conduit for the transmission of pressure and it is difficult to be certain which component is the major site of resistance during flow.

Staub has studied the morphology of pulmonary edema induced either by increased hydrostatic pressure or by alteration of capillary permeability; the sequence of change as viewed with light microscope appears to be the same, although differing physiologically (11). His studies were made possible by the development of techniques for rapidly freezing tissues in situ and retaining anatomic relationships during fixation (as water is removed) by substitution (12) or by freeze-drying. As pulmonary edema develops, fluid initially accumulates in the loose connective tissue of the interstitium surrounding extra-alveolar arterioles, venules, and airways, followed by thickening of the alveolar walls. Only after filling of the interstitial compartment has occurred does fluid appear in alveolar spaces. As edema progresses, alveoli are seen to contain little or no fluid or are completely fluid filled; intermediate stages of filling are not observed, suggesting that this transition is extremely rapid. The tendency for alveoli to collapse or fill with fluid is referred to as "alveolar instability" and is the hallmark of pulmonary edema.

The resolution of pulmonary edema is more varied than its onset and depends, in large part, on the cause of edema formation. Pulmonary lymph flow can increase at least 4-fold during acute edema production but is insufficient to handle large volumes of fluid (13, 14). In chronic states lymph flow may increase further; this adaptive mechanism is thought to permit patients with mitral stenosis to live without pulmonary edema despite wedge pressures above 24 mm Hg (15). In the resolution of acute pulmonary edema, however, lymphatic drainage must play a relatively minor role. In hydrostatic pulmonary edema, such as demonstrated by Case 1, improvement is usually dramatic when the capillary bed is decompressed, re-establishing the normal gradient for absorption of alveolar fluid. Electron microscopic studies of the alveolocapillary membrane during hydrostatically induced pulmonary edema have shown no major structural alteration although focal areas of rupture, causing alveolar hemorrhage, may occur (16). Thus, the low protein transudate is rapidly reabsorbed into pulmonary capillaries through a basically intact membrane.

On the other hand, if the endothelium becomes permeable to larger molecules, principally protein, the colloid osmotic pressure in the interstitial space may approach that of the capillary and pulmonary edema will develop at normal levels of hydrostatic pressures. The morphology of pulmonary edema following damage to the

alveolo-capillary membrane with altered permeability is less clear. It appears that altered capillary permeability may have varied anatomic features and presumably different mechanisms. In all forms of such edema, large blebs are found in the cytoplasm of the endothelial cells but other evidence of cellular damage may or may not be conspicuous. Attempts have been made to demonstrate the site of vascular leakage with electron microscopic marker particles. Karnovsky has shown that small particles such as horseradish peroxidase (mol wt 40,000) traverse the normal endothelial cell intercellular junctions but are retained by tight epithelial intercellular junctions (17, 18). Ferritin (mol wt 500,000) is apparently slowly transported across the cells via pinocytotic vesicles. Following exposure to noxious agents the site of vascular leakage may be either transcellular or intercellular, depending on the inciting agent and likely also the size of the marker employed (17). Pulmonary edema resulting from abnormal capillary permeability is characteristically of high protein content and fibrin may be histologically identified in the alveolar spaces. Removal of intra-alveolar protein is necessary to reestablish osmotic gradients and alveolar structure. Intact protein may be removed from the alveolar spaces either by lymphatics or by entering capillaries directly although at a very slow rate compared to water (20, 21). The transfer of protein from the alveolar space to the capillary probably depends on transport via pinocytotic vesicles through both alveolar epithelial and endothelial cells. Since the agent producing pulmonary edema presumably damaged these cells to cause the development of edema, reabsorption is likely to be similarly impaired. It has been suggested that protein in alveolar spaces must be enzymatically degraded before removal (20). However, Liebow has demonstrated that heterologous serum albumin appears antigenically intact in the peripheral circulation following deposition in the lung (22). While alveolar macrophages are known to ingest protein, their role, and the role of the mucociliary system in the quantitative removal of alveolar protein is unclear.

Thus, it would be predicted that the clearing of alveolar fluid following damage to the alveolo-capillary membrane would vary greatly, depending on the extent of membrane damage, the protein content of the fluid, and the degree of organization of the extravasated material.

Case #2: [redacted]

This 30-year-old woman was brought to the EOR in moderate respiratory distress following mouth-to-mouth resuscitation after she nearly drowned in a fresh water pool. On arrival in the EOR, she was cyanotic with a respiratory rate of 45/minute, and was coughing up bright red blood. Initial blood gases on an unknown concentration of inspired oxygen were: pH 7.20, pCO_2 36, pO_2 146, and O_2 saturation 100%. Chest radiograph showed bilateral alveolar

infiltrates with a normal heart. She was admitted to the MICU for observation. Treatment consisted of continuous 40% oxygen mist via face mask and intermittent assisted ventilation achieving tidal volumes in excess of 1500 mls.

The chest radiograph rapidly cleared and 2 days after admission the patient's arterial pO_2 was 81 mm Hg while breathing air. She was discharged on the 3rd hospital day and on a follow-up visit to the clinic one week later was virtually asymptomatic.

Diagnoses: 1. Pulmonary edema due to fresh water drowning. 2. Metabolic acidosis secondary to hypoxia.

The aspiration of water or saline produces pulmonary edema and endothelial and epithelial lesions identical to those produced by hydrochloric acid although differing in the extent of damage (23). Alveolar hypoxia produces similar structural lesions, also associated with pulmonary edema and hemorrhage (24). Reflex pulmonary hypertension, which follows the aspiration of fresh water (25), may have contributed to the formation of pulmonary edema in this patient. The diffuse infiltrates noted radiographically in human near-drowning victims appear to be due principally to the exudation of intravascular fluid, not aspirated fluid, since such individuals usually aspirate only small amounts of fluid (26). Further, the onset of acute respiratory distress may be delayed up to 12 hours following submersion (27), a lag time seen with many agents which damage the alveolo-capillary membrane. The relatively benign clinical course of this patient indicates that despite the presumably nonhydrostatic nature of her pulmonary edema resolution occurred promptly.

However, at the time of admission to the EOR she demonstrated the principal features of all patients who have fluid in alveolar spaces; decreased lung compliance and hypoxemia due to shunting. These changes are explained by the concept of alveolar stability as defined by the work of Clements and other investigators (28-31). Assuming the alveolus to be spherical in configuration and basically an air filled bubble with a liquid lining, the pressure required to keep the bubble from collapsing is related to the surface tension of its walls and its radius, through the LaPlace theorem:

$$P = \frac{2\,T}{R}$$, where P is the transmural pressure, T is surface tension, and R is the radius of the bubble.

When transpulmonary pressure is low, such as at low lung volumes, alveoli with high surface tensions, or with small radii, will be "unstable", i.e., will collapse. Fluid in the alveolar space may

interfere with alveolar surfactant, thus raising surface tension, or may cause collapse only by changing the dimensions of the alveolus. Once collapse has occurred, high pressures will be required to reopen the alveolus. Cook et al have shown that in pulmonary edema the elastic behavior of lung tissue is normal and that the decreased compliance observed can be largely overcome by forced inflation to large lung volumes (32). Said et al have demonstrated that the hypoxemia accompanying pulmonary edema is due to shunting; in their studies shunting was markedly reduced by forced inflation to large lung volumes (33). In both studies, the improvement noted following large inflations was transient and the abnormalities returned when breathing at usual tidal volumes was restored. Similar changes are found in humans with acute pulmonary edema (34). These observations are consistent with the concept of the unstable alveolus; following alveolar collapse shunting occurs as blood flow continues to perfuse nonventilated alveoli. The severity of alveolar instability may be influenced by the nature of the alveolar fluid and its effect on surfactant but the basic abnormality is due to the presence of such fluid alone and thus a similar sequence of events occurs in pulmonary edema of any cause.

Case #3: [redacted]

This 29-year-old man was found unconscious in his hotel room an unknown time following ingestion of large quantities of multiple sedative and tranquilizing drugs. On admission to the EOR, he was cyanotic with minimal respiratory efforts. During tracheal intubation, copious secretions and gastric contents were noted distal to the larynx. Diffuse rales were heard throughout the chest. Arterial blood gases initially were: pH 7.38, pCO_2 39, pO_2 38, 79% saturation; on IPPB with an F_{IO2} of 70%, repeat blood gases showed: pH 7.38, pCO_2 41, pO_2 92, 94% saturation. A radiograph of the chest showed bilateral diffuse alveolar infiltrates.

Initial treatment consisted of intravenous and endotracheal hydrocortisone, antibiotics, vigorous fluid administration, and continuous assisted ventilation via IPPB, providing tidal volumes of 1.0 to 1.5 L. and frequent sigh volumes of 2.5 to 3.0 L. A 70% F_{IO2} was required to maintain the arterial pO_2 in the range of 50 to 60 mm Hg. Although the patient regained consciousness after 24 hours, his course was complicated by upper gastrointestinal hemorrhage and progressively more severe hypoxemia until, on the 4th hospital day, the arterial pO_2 was 44 with an F_{IO2} of 90%. Increasing dead space ventilation and increasing right to left shunting, with stable but low compliance (effective dynamic compliance = 40 ml/cm H_2O) suggested pulmonary embolism; a Jude umbrella was inserted in the inferior vena cava via the right internal jugular vein. Although he was never hypotensive, the

patient's central venous pressure remained in the range of 20 to 25 cm H_2O. The patient continued to deteriorate and expired on the 13th hospital day.

A limited autopsy revealed the lungs to be firm, virtually airless, and yellow-gray in color. The IVC umbrella was occluded by thrombi but none were identified in the pulmonary vessels.

Diagnoses: 1. Massive acid aspiration pneumonitis. 2. Superimposed pulmonary oxygen toxicity.

It is important to note that although the outcome of Case 3 differed markedly from Cases 1 and 2, the initial clinical presentation of the acute pulmonary process was very similar. The ultimate prognosis of these patients may depend greatly on the nature of the aspirated fluid, or the cause of edema formation, and this may be difficult to establish in a clinical situation. In Case 3, the finding of gastric contents in the distal trachea strongly supports the diagnosis of acid aspiration.

The deleterious effects on the lungs of acid instillation were first systematically studied by Winternitz in 1920 as corollary studies to an investigation of the effects of war gases (35). He noted that extensive vascular congestion, pulmonary edema, and hemorrhage occurred promptly after the instillation of acid followed by epithelial proliferation during the reparative phase and he probably described the formation of hyaline membranes. Mendelson reported 66 cases of acute respiratory distress due to the aspiration of gastric contents during obstetric anesthesia (36). In experimental studies in rabbits he demonstrated that the acute diffuse form of lesion was due to hydrochloric acid although the only two fatalities which occurred in his clinical series were due to airways' obstruction by particulate matter. Teabeaut confirmed the pathologic findings of Winternitz and conclusively showed that the diffuse hemorrhage and edema were related to the pH of the fluid instilled; material of pH of less than 2.4 produced the lesion while materials of higher pH, regardless of other composition, did not (37). Subsequent studies using more sophisticated techniques have built on these basic observations and have defined the physiologic and ultrastructural changes which accompany acid aspiration. In brief, following the intrabronchial instillation of 4 cc/kg of 0.1 N HCl, a uniformly lethal aspiration model in the dog, cardiac output, and blood pressure transiently fall and then return to baseline levels; pulmonary vascular resistance and lung weight begin a steady rise; hypoxemia unrelieved by breathing oxygen develops rapidly and becomes progressively more severe; lung compliance falls steadily; as mixed metabolic and respiratory acidosis intervene the animal dies, usually within one-half to 8 hours after instillation (38-46). Electron microscopically,

necrosis of the endothelium and epithelium is seen, the latter involving both Type I and Type II alveolar cells (23, 46). Varying degrees of hemorrhage, edema and atelectasis are found with alveolar spaces being filled with proteinacous, fibrinous, and cellular debris. Hyaline membranes appear in alveoli after 48 hours even in the absence of oxygen therapy.

This histologic picture apparently represents the limited spectrum of response of the lung to agents which damage the alveolo-capillary membrane, particularly the endothelium. Similar changes are observed following injury induced by smoke, hydrocarbons, metallic fumes, toxic gases like NO_2, chlorine, and ozone, and a variety of inhaled chemical compounds (47-52). Oxygen in high inspired concentrations produces identical changes (53-56).

The occurrence of widespread atelectasis, edema, and hemorrhage suggests that surfactant deficiency may be a major factor in the pathogenesis of this lesion. Favoring this concept is the observation that the surface tension lowering activity (an index of surfactant activity, not gravimetric concentration) is reduced in atelectatic as well as hemorrhagic areas of such lungs (46). This reduction occurs rapidly suggesting that surfactant has been inactivated or displaced from the air-fluid interface. Quantitatively, phospholipids with high surface tension lowering activity are reduced to only about 50% of normal levels in the lungs of infants with neonatal respiratory distress, and the amount remaining would be more than sufficient to generate an alveolar lining layer, if available, suggesting that inactivation is the principal mechanism producing lowered surfactant activity (57). Surfactant is produced by the alveolar Type II cells, or granular pneumocytes, and is one of the products of very active lipid metabolism by the lung. The half time of surfactant in small animals, as estimated from studies with radioactive precursors, is about 14 hours (58); Clements has estimated that in man a similar value would be approximately 2 days (59). These estimates agree reasonably well with the time course of the disappearance of surfactant activity following ligation of a pulmonary artery in the absence of gross infarction and hemorrhage (60-61). Thus, reduced blood flow may inhibit the production of surfactant and lead to a quantitative deficiency over a period of several days (62). Since evidence of capillary damage with leakage of blood or plasma into alveolar spaces always accompanies the acute injury and plasma proteins inactivate surfactant (63, 64), it is difficult to distinguish the effects of the damaging agent on surfactant from its effects on capillary integrity. It is probably safe to say that a primary deficiency of surfactant has not been demonstrated as the cause of any clinical disorder.

The same sequence of capillary damage, edema, hemorrhage, and alveolar collapse may follow injury by intrinsic mechanisms. A great deal of recent investigation has been stimulated by the occurrence of pulmonary complications following nonthoracic injuries in Vietnam although such complications have been well documented and studied previously (65-68). Evidence of lung damage usually, but not always, follows a period of clinical shock. The mechanism of lung endothelial damage which occurs in these casualties is unclear but appears to involve circulating leukocytes which become fused to the endothelium before capillary disruption is demonstrated (69). The role of platelets, vasoactive materials such as histamine, serotonin, and polypeptides, and possibly undefined humoral substances is an area of speculation at the present time. Embolism of fat or other microparticulate matter to the lung results in the same basic pathology, differing mainly in the extent of injury produced by different agents (70, 71). Disruption of alveolar capillaries by direct thoracic trauma produces the same initial lesion; the progressive nature of pulmonary contusion clinically (72-75) emphasizes the need for an aggressive therapeutic approach aimed at correcting the basic alteration, fluid in the alveolar spaces.

Case #4: [redacted]

This 25-year-old man was admitted with a 3-day history of a vesicular, hemorrhagic, and pustular cutaneous eruption, and a 2-day history of pleuritic chest pain, dyspnea and cough. His children had all recently had chicken pox, with the initial case occurring approximately 3 weeks prior to the patient's admission. On admission the BP was 110/70, P 110, T 100°, RR 62. There were bilateral crepitant rales at the lung bases. Hemoglobin was 19 gm% with a hematocrit of 60. Admission blood gases were: pH 7.48, pCO_2 34, pO_2 38, 59% saturation. Because of difficulty in obtaining adequate oxygenation, a tracheostomy was performed on the 2nd hospital day. Approximately 12 hours after this procedure a tension pneumothorax developed on the left which ultimately required two chest tubes for adequate re-expansion of the lung. Treatment consisted of intravenous fluids, antibiotics, and continuous IPPB with tidal volumes of between 3 and 4 L. On this program the patient's effective dynamic compliance improved from 30 to 50, and ultimately to 70 ml/cm H_2O. Blood gases on the 2nd hospital day, while breathing 100% oxygen were: pH 7.49, pCO_2 27, pO_2 46, 58% saturation. CPPB was applied but did not improve oxygenation. Four days after admission, the patient suddenly became hypotensive, his tidal volumes decreased markedly, and he rapidly expired. Postmortem radiograph of the chest revealed a tension pneumothorax on the right.

Diagnoses: 1. Varicella pneumonia. 2. Tension pneumothorax.

Viral pneumonia produces the pathologic lesions characteristic of diffuse alveolar injury. Influenza is by far the most common infectious etiology but other viral etiologies have been reported (76-82). In Case 4, an attempt was made to reverse the physiologic abnormalities by administering large tidal volumes. As predicted from experimental studies, his compliance improved with this procedure. The absence of a corresponding improvement in oxygenation indicates that the large tidal volumes were achieved principally through overexpansion of more normal regions of lung; the persistent large shunt indicated that a number of perfused but non-ventilated alveoli remained. Overexpansion of normal areas of lung may have been instrumental in the development of the pneumothorax which caused his death.

Since the shunt effect might have been due to alveoli which collapsed at low transpulmonary pressures, continuous positive pressure breathing (CPPB) was employed. Although not a new technique, the application of CPPB in patients with respiratory distress has become popular over the last several years. The principal differences between CPPB, IPPB, and expiration retardation are demonstrated in Figure 2. With IPPB, as administered with any of the pressure or volume limited respirators, airway pressure is positive during inspiration but falls to atmospheric or zero at the end of expiration. Exhalation retardation prolongs the period of expiration but end-expiratory pressure still falls to zero if the patient's respiratory rate is sufficiently slow. In CPPB, a continuous level of expiratory pressure is maintained on the airway. This pressure may be provided by connecting the exhalation valve of the ventilator to an underwater seal with large bore tubing; the magnitude of the end-expiratory pressure is determined by the depth to which the tubing is inserted beneath the surface of the water. Alternatively, a spring-loaded valve can be employed in the exhalation port (83). The level of sustained end-expiratory pressure is shown on the manometer of the ventilator. If the desired end-expiratory pressure is not held steadily between respiratory cycles, the system is leaking. The successful application of this technique requires that the patient's ventilation be controlled by the ventilator. Attempts by the patient to initiate inspiration will drop airway pressure below zero and negate the effect of CPPB.

The physiologic effects of maintaining a positive airway pressure throughout the respiratory cycle in the treatment of pulmonary edema was studied in 1938 by Barach in both experimental animals and patients (84). He also reviewed the literature on the application of CPPB back into the nineteenth century. Barach attributed the striking improvement in the cardiogenic pulmonary edema of his patients following the application of CPPB to decreased venous return. Sharp et al in 1961 reported detailed studies of lung mechanics in patients with pulmonary edema treated with CPPB (85).

They noted that compliance increased following CPPB even though tidal volume remained the same and attributed this effect to an increase in the resting end-expiratory volume (FRC) of the lung, although they did not make these measurements. Recent studies following the rebirth of CPPB have demonstrated that such an increase in lung volume does occur following the application of this technique (86). The effect of this volume change on lung compliance in pulmonary edema is demonstrated in Figure 3. Compliance is normally linear throughout most of the lung volume. With the development of pulmonary edema, the initial segment of the compliance curve becomes flattened indicating that segments of the lung have collapsed at low lung volumes, requiring higher pressures to reopen them. When these areas have reopened, compliance may be nearly normal. Maintenance of positive end-expiratory pressure prevents the lung from returning to the volume at which alveoli collapse; thus compliance is improved and shunting is diminished.

Case #5: [redacted]

This 16-year-old boy collapsed while cleaning a poorly ventilated petroleum tank. He was seen to vomit by observers who dragged him from the tank. He was unconscious on admission to a hospital in [redacted] where an emergency tracheostomy was performed and IPPB therapy initiated. A chest radiograph showed diffuse pulmonary infiltrates. The patient rapidly regained consciousness but continuous IPPB with an F_{IO_2} of 60% was required to maintain the arterial pO_2 at approximately 40 mm Hg. Treatment included steroids, gentamicin, cephalothin, digitalis and diuretics. He was transferred to Parkland 6 days after the incident. On admission, he became rapidly tachypneic and cyanotic after a few seconds off IPPB. Examination of the chest revealed tubular breath sounds throughout. Cultures of sputum contained Proteus mirabilis and Pseudomonas species. During 4 days in the hospital, an increasing F_{IO_2} was required to maintain oxygenation despite CPPB. On the 4th hospital day, while breathing an F_{IO_2} on IPPB of 100%, the arterial pO_2 was 46 mm Hg. Cardiac arrest occurred later that day and the patient could not be resuscitated.

Diagnoses: 1. Diffuse pneumonitis due to inhalation of petroleum (probably gasoline) vapor. 2. Questionable acid aspiration pneumonitis.

A major consideration underlying the therapeutic approach to patients with diffuse alveolar injury must be the potential reversibility of the lesion. Early interstitial fibrosis and organization of intra-alveolar material was present in the fatal cases presented within a few days of the initial injury. No comprehensive long-term follow-up studies are available in adults who have sur-

vived the syndrome although one patient with diffuse fibrosis following acid aspiration has been reported (87). Long-term changes apparently do occur in infants following successful therapy of neonatal respiratory distress in high oxygen environments (88). These changes tend to disappear in time suggesting that the lungs of infants, at least, have a considerable capacity for repair.

The detailed study of oxygen toxicity in primates has provided the best insight into the reparative processes of the lung subsequent to diffuse alveolar injury (89, 90). Following a period of acute edema, hemorrhage, and alveolar collapse which develops after about 72 hours of 100% oxygen breathing surviving animals improve and return to a normal state clinically while still maintained in the 100% oxygen atmosphere. At this stage, the alveoli are lined by cuboidal epithelium composed entirely of Type II alveolar cells, a change which has been noted in virtually all experimental models of diffuse alveolar injury, as well as in patients with this syndrome. It has been proposed recently that this alteration represents a transformation of Type I alveolar cells into Type II cells (91). More likely, the Type I cells, which possess a large exposed surface area but apparently little metabolic machinery, are destroyed, and the Type II cells proliferate to replace the alveolar epithelium (90). This sequence would be consistent with the data of Bertalanfy who also noted the greater capacity for division of the Type II alveolar cells (92).

In the primate studies it was necessary to gradually reduce the concentration of inspired oxygen as a sudden return to air breathing produced cyanosis and respiratory distress. However, 2-3 months after returning to air breathing the lungs of the animals were nearly normal, showing only patchy areas of fibrosis and thickening of the alveolar walls (90). Similar studies after other types of lung injury are needed but, at the present time, it appears justified to assume that the acute pathologic changes associated with diffuse alveolar injury will largely resolve and that surviving patients will have at least adequate pulmonary function to sustain life.

Case #6: [redacted]

This 27-year-old man was admitted to the EOR in marked respiratory distress. A sketchy history was later assembled which included an evening of heavy drinking and possibly the intravenous injection of heroin. Blood gases on admission were: pH 7.10, pCO_2 65, pO_2 45, saturation 73%. Endotracheal intubation was immediately performed and vomitus was noted in the hypopharynx. A chest radiograph revealed bilateral diffuse alveolar infiltrates. Initial therapy included IV fluids, aramine, steroids, antibiotics, and continuous IPPB. On the day following admission the patient

remained severely hypoxemic with an arterial pO_2 of 80 mm Hg while breathing 90% oxygen. Succinylcholine was administered to control the patient's respiratory pattern. CPPB, with an end-expiratory pressure of 10 cm H_2O was applied; this procedure allowed the F_{IO_2} to be decreased to 40% with the arterial pO_2 maintained at 48 mm Hg. However, over the next two days increasing concentrations of inspired oxygen were required to maintain the arterial pO_2 in the range of 50 mm Hg. Four days following admission, the patient was placed on a Lande membrane oxygenator with a veno-venous shunt providing a 4 liter/minute flow of oxygenated blood. The inspired oxygen concentration used to ventilate his lungs during this period of extracorporeal oxygenation was reduced to 30%. Systemic heparin was administered while the patient was on the membrane oxygenator. Approximately 14 hours after being placed on the oxygenator he developed fixed dilated pupils and bilateral plantar extensor responses. These neurological findings remained unchanged and the membrane oxygenator support was discontinued. The patient expired 24 hours later.

A brainstem hemorrhage was found at autopsy. The lungs were virtually airless, and deeply congested.

Diagnoses: 1. Massive acid aspiration pneumonitis. 2. Possible heroin-induced pulmonary edema.

Pulmonary edema following the injection of heroin may occur abruptly or after a several hour lag period; may produce fulminant symptoms or be incidentally detected radiographically; and usually responds to oxygen therapy alone although some investigators advocate the use of morphine antagonists in low doses (92-94). The subsequent course of this patient, however, suggests that he had aspirated large quantities of acid gastric contents during the period of CNS depression. With the exception of transient improvement in oxygenation when CPPB was first applied, his course was inexhorably progressive.

The use of an extracorporeal oxygenation system in this patient was predicated on the assumption that his lungs would recover if the patient could be kept alive. Long-term extracorporeal oxygenation was not feasible until the development of membrane oxygenators (95-98). In membrane oxygenators, direct contact of blood and bubbles of oxygen is avoided with the result that much less destruction of blood occurs (99). Although blood flow through a single membrane unit is limited, increased flow of oxygenated blood can be obtained by connecting several units in parallel. With the Lande unit, as employed in this patient, blood which has not been adequately oxygenated on a single pass through the membrane can be recycled. A veno-venous shunt was used in this patient with oxygenated blood being returned to the superior vena cava.

This technique provides a better distribution of oxygenated blood than return to the arterial system. The pO_2 of blood leaving the oxygenator was between 200-400 mm Hg at a flow of 4 liters/minute resulting in an arterial pO_2 between 60-80 mm Hg while ventilation of the patient's lungs was continued with nontoxic levels of inspired oxygen. Unfortunately, systemic heparinization is required with present units and the patient's death can be directly attributed to anticoagulation. However, the institution of a successful oxygenation support system for a significant period of time holds the promise that further developments in this area will make extracorporeal oxygenation a practical therapeutic adjunct for patients with reversible respiratory insufficiency.

Although the various modes of therapy available were demonstrated in case presentations, it would be useful to review them separately.

A. Supportive Therapy

1. Oxygen

Death during the first few hours after the onset of acute pulmonary edema due to diffuse alveolar damage is due to tissue hypoxia produced principally by the inability of the lung to fully oxygenate the blood (arterial hypoxemia) although cardiac output may be reduced in some patients and oxygen released to tissues may be impaired by carbon monoxide in patients following smoke inhalation. Alveolar hypoventilation may contribute to the hypoxemia in patients with central nervous system depression. As previously discussed, hypoxemia is due mainly to right to left intrapulmonary shunting and thus responds poorly to oxygen administration alone. Oxygen should be used in high concentrations initially however. The aim of oxygen therapy is to restore the arterial pO_2 to approximately 60 mm Hg; at this level, corresponding to approximately 90% saturation of hemoglobin, tissue hypoxia is relieved (100). In this circumstance, as in all others, fear of pulmonary oxygen toxicity should not limit the use of oxygen in the concentration required to oxygenate the patient's tissues.

2. Intermittent positive pressure breathing (IPPB)

IPPB may be of benefit to the patient in pulmonary edema through several different mechanisms; decrease in the work of breathing and thus reducing the need for cardiac output and oxygen delivery, decrease in the pulmonary intravascular blood volume and possibly decreased venous return to the right heart, and, if large tidal volumes are administered, atelectatic areas of lung may be reopened. The latter mechanism provides the major source of improvement in both lung mechanics (increased compliance) and gas exchange (decreased shunting)(32, 33) and is probably the

most significant factor in the early treatment of patients with diffuse alveolar injury. However, to be effective, large tidal volumes of 15 ml/kg or greater must be achieved. This may require endotracheal control of the airway, sedation with morphine, or muscular relaxation with drugs like succinylcholine and curare in tachypneic, restless patients. Significant respiratory alkalosis should be avoided by slowing the respiratory rate, addition of dead space, or possibly the addition of CO_2 to inspired gas. Clements argues against the use of very large tidal volumes, such as were employed in Case 4, because of a deleterious effect on the conservation of surfactant (59). When a surfactant film is maximally extended, all available molecules are brought to the surface; subsequent compression causes some molecules to be extruded, thus wasting the limited surfactant reserves. He suggests that both extremes of lung volume, atelectasis or overexpansion, should be avoided in the management of patients with diminished surfactant.

The value of immediate positive pressure inflation in diffuse alveolar injury has been best demonstrated by Cameron et al in studies of experimental acid aspiration (101). They instilled 2 cc/kg of 0.1 N HCl into the right mainstem bronchus in dogs; 15 of 18 untreated control animals died, while no fatalities occurred among 9 animals which received IPPB for six hours beginning immediately after acid instillation. An additional group of 10 animals received IPPB for six hours beginning 24 hours after acid instillation; their outcome was identical to that of the controls. Initial radiographic and physiologic changes were similar in all groups. In animals which survived, radiographic evidence of consolidation began to clear after 3 to 4 days, accompanied by a return of blood flow as demonstrated by lung scans. It seems likely that the beneficial effect of IPPB was due to reopening of lung regions which had been only partially damaged. In the absence of prompt reopening irreversible changes occurred in these regions as well. Delayed changes in the lung following aspiration are not due to acid per se as other investigators have shown that the pH of instilled material is buffered within minutes (42). These findings suggest that the structural lung injury occurs virtually immediately and that subsequent deterioration in pulmonary function is due to the continuing effects of nonreabsorbed alveolar fluid and collapse.

3. Continuous positive pressure breathing (CPPB)

A number of investigators have recently reported the application of CPPB in patients with diffuse alveolar injury of various etiologies (102-108). CPPB administered via endotracheal tube or continuous positive airway pressure (CPAP) (without ventilatory support) via a chamber enclosing the head and sealed at

the neck has been reported to improve lung function in infants with a neonatal respiratory distress syndrome (109, 110). Enclosing the chest of such infants in a negative pressure chamber, which has the same physiologic effect as CPPB, also has been reported (111). Complications arising from the use of CPPB have received relatively scant attention in the literature. Pneumothorax has been seen in approximately 50% of patients in whom CPPB has been used at Parkland Hospital, and subcutaneous and mediastinal emphysema are even more common. Elevation of venous pressure, reduced cardiac output, and reduced blood pressure must be carefully watched for during the initial application of CPPB. However, due to the noncompliant stiff lungs of these patients, pressure applied to the airway may not be reflected by a rise in intrathoracic pressure and significant hemodynamic changes are not frequently seen. Our technique is to begin with 5 to 8 cm H_2O pressure, follow the central venous pressure, heart rate, and blood pressure and recheck arterial blood gases after 15 to 20 minutes. If no improvement in oxygenation has occurred, and no adverse hemodynamic changes have been noted, the level of CPPB is increased in stepwise fashion to a maximum of about 15 cm H_2O. It is important to emphasize that if CPPB is considered, the patient must be in a facility where he can be carefully monitored, the occurrence of complications promptly recognized, and accurate measurements of arterial and inspired oxygen tensions obtained.

4. Other supportive measures

Left ventricular failure does not appear to contribute to the development of the initial lesion in patients with diffuse alveolar injury and digitalis is not recommended. Although many patients show evidence of hemoconcentration initially due to the loss of plasma into alveolar spaces, vigorous fluid replacement may further aggravate the pulmonary lesion. As in other clinical states, the central venous pressure is an unreliable indicator of the patient's capability to tolerate fluid loads (112). However, volume expansion may alleviate hypotension associated with CPPB (105). Diuretics are likely to further reduce the intravascular volume without influencing the intrapulmonary extravascular fluid leading to hypotension and should accordingly not be used in the acute phase. Prompt endotracheal lavage following aspiration has been recommended. Since aspirated fluid appears at the pleura within 18 seconds (40) and pH of the material is rapidly raised by intrinsic buffers (42), such lavage will accomplish little except to move tracheal contents more distal in the lung and add to the volume of alveolar fluid already present.

B. "Specific" Forms of Therapy

1. Corticosteroids

Intratracheal and/or parenteral administration of corticosteroids has been widely recommended to reduce the inflammatory reaction following acid aspiration. The enthusiasm for this therapy stems from several early experimental studies and case reports which demonstrated a beneficial effect (113-115), despite other investigations which failed to find such benefit (42). In general, this reviewer found the negative studies to have been more carefully performed and documented. One interesting study of acid aspiration, utilizing isolated perfused lung lobes, found that lobes treated with Prodecadron (unfortunately a combination of isoproterenol and dexamethasone) accumulated less edema than control lobes (44). Clinical reports of beneficial effects of corticosteroid therapy must be interpreted with caution; aspiration pneumonitis is a highly varied process depending principally on the pH of the aspirated material which is rarely known under clinical circumstances. Steroids have been stated to be dramatically effective in patients with respiratory distress subsequent to fat embolization (102) and near-drowning (116). Although employed by many investigators, steroid therapy has received less enthusiasm in the treatment of severe viral pneumonia.

If steroids are to have any effect on the initial lesion, it is apparent that they must be administered soon after the lung insult. Our preference has been to employ parenteral steroids for acid aspiration if treatment is begun within 24 hours. Hopefully, the mechanism of action and indications for use of steroids will be soon evaluated in appropriate animal models.

2. Antimicrobial agents

In the absence of a primary infectious process, diffuse alveolar damage is a sterile lesion and antimicrobial agents are not required in initial therapy. In both patients and experimental animals, virtually all agents which produce this syndrome markedly impair the bactericidal defense mechanisms of the lung and superinfection, usually with gram-negative bacilli, is common. Great care must be exercised in the care of such patients to minimize the risk of infection and daily specimens of tracheal aspirates should be examined by smear and culture. Antimicrobial therapy is best deferred until infection is demonstrated.

3. Surfactant replacement

A few attempts have been made to replace alveolar surfactant by aerosolizing phospholipid material into the lung (117-119)

but this approach has not been adequately explored experimentally and does not appear ready for clinical application, despite the technical capability of generating aerosols which are highly surface active (120).

4. Other agents

Even less well understood than surfactant is the role of various chemical mediators, such as histamine and serotonin, and the vasoactive polypeptides in the production and progression of acute diffuse alveolar injury. No clinical information about these substances, or their antagonists, in this syndrome is available.

Pulmonary vascular thrombosis has been observed in both patients and experimental models of this syndrome. The frequency of this complication has varied widely and routine anticoagulation of such desperately ill patients is not recommended.

C. Extracorporeal Oxygenation

Although virtually all of the reported patients in whom prolonged extracorporeal oxygenation has been attempted have ultimately died, this technique offers a promising therapeutic adjunct for the future. Basic research is needed along several lines before the potential usefulness of this technique can be evaluated. Improvements in oxygenator design, particularly to avoid the necessity of systemic heparinization, are being explored. A better understanding of the natural history of diffuse alveolar injury by various causes is required.

Finally, as in all of medicine, an ounce of prevention is worth a pound of cure. In the case of acid aspiration, the ounce may be one of an appropriate antacid (121).

SUMMARY

The syndrome of dyspnea, tachypnea, hypoxemia, decreased compliance, and diffuse alveolar infiltration in the absence of left ventricular failure may be caused by diffuse alveolar damage from a number of inhaled, aspirated, or endogenous toxic materials. The basic physiologic disturbances are explained by alterations in the fluid equilibrium of the lung with "unstable alveoli" being the hallmark of the disease. Treatment is mainly supportive with the aim of preventing death from hypoxia and to prevent irreversible changes in collapsed or protein filled alveolar spaces. If the patient survives the acute process, the prognosis for return of nearly normal pulmonary function appears excellent.

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FIGURE 1

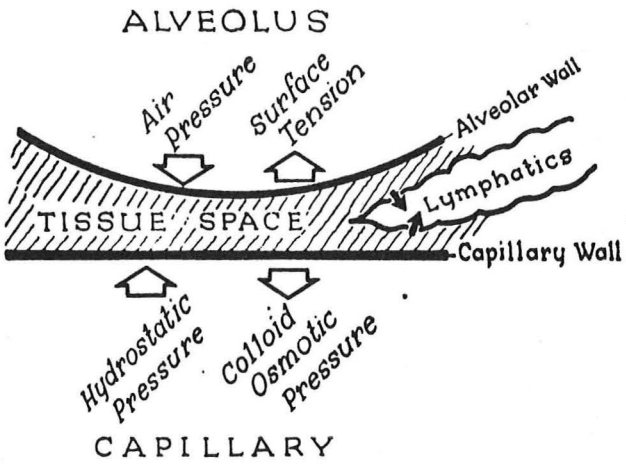

ALVEOLUS
Air Pressure
Surface Tension
Alveolar Wall
Lymphatics
TISSUE SPACE
Capillary Wall
Hydrostatic Pressure
Colloid Osmotic Pressure
CAPILLARY

FIGURE 2

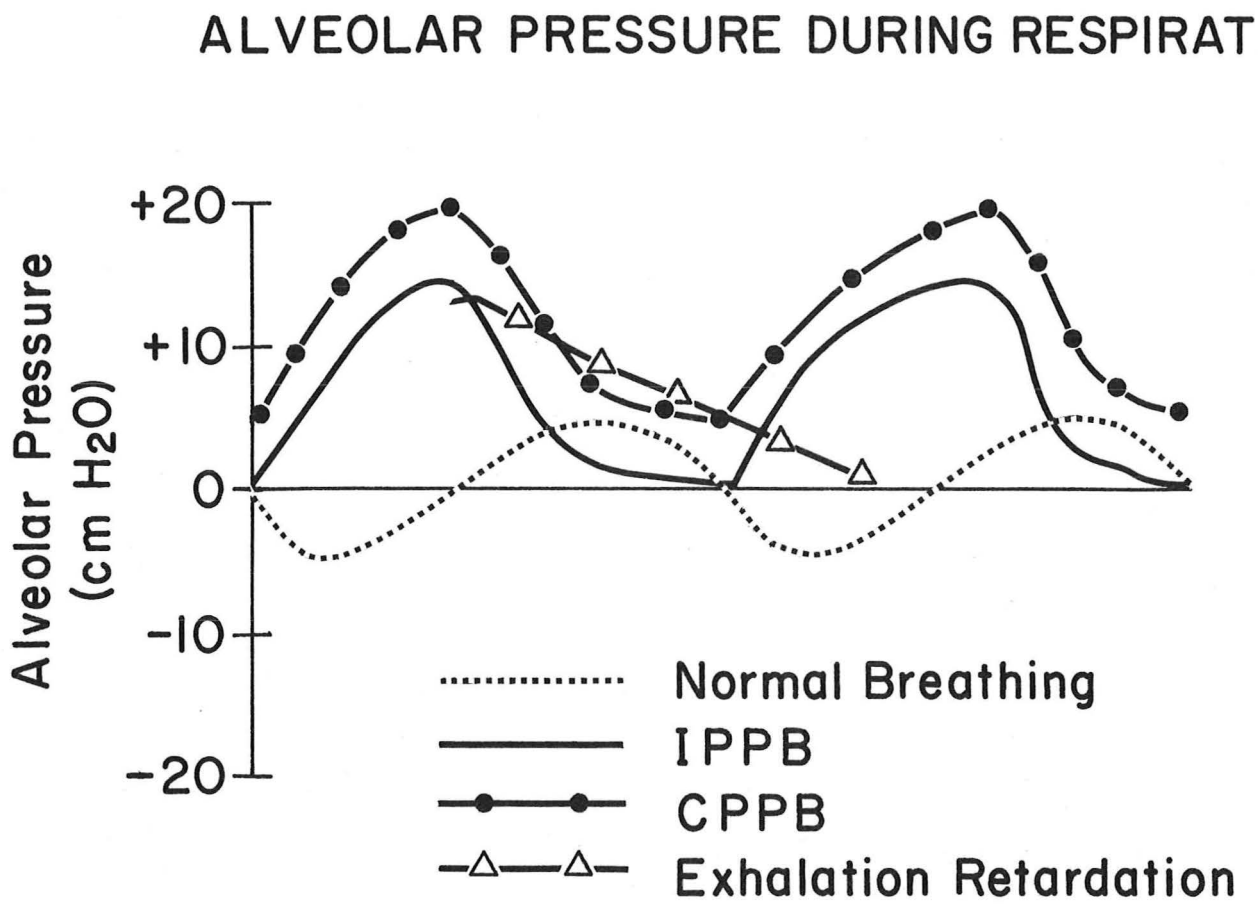
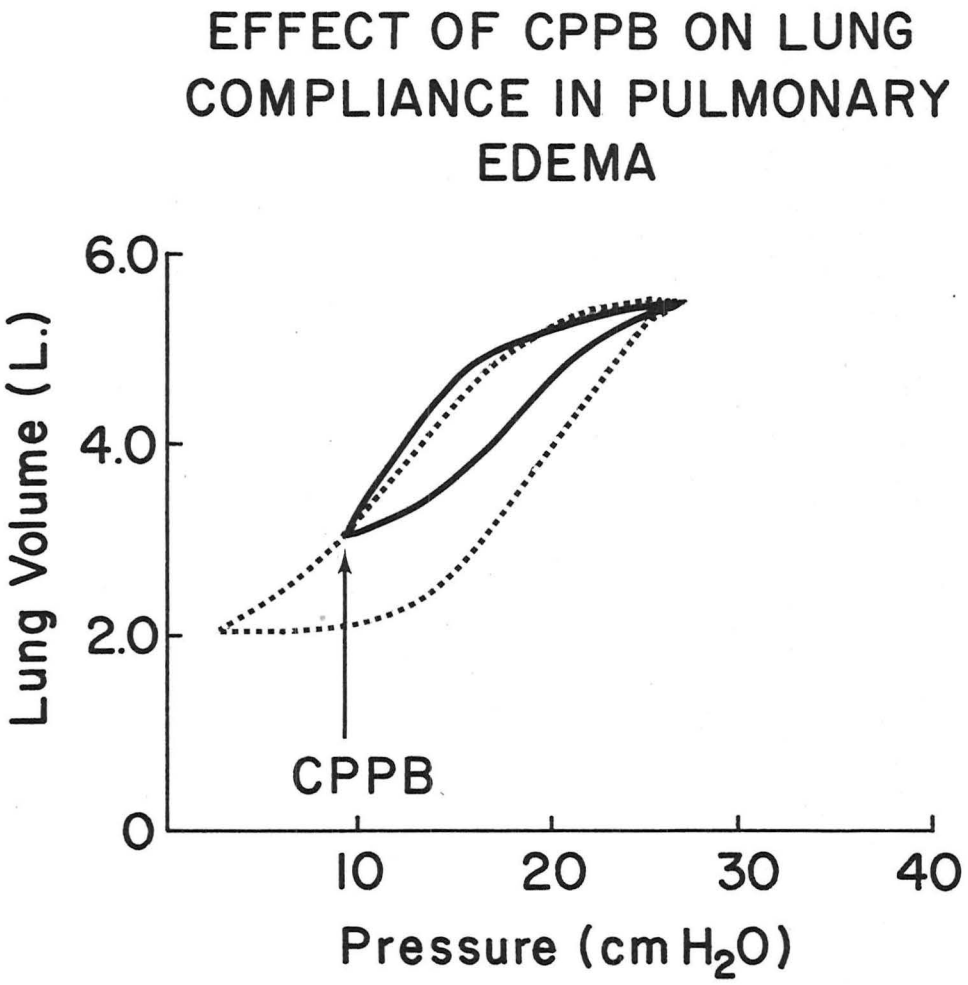

ALVEOLAR PRESSURE DURING RESPIRATION
Alveolar Pressure (cm H2O)
+20
+10
0
-10
-20
Normal Breathing
IPPB
CPPB
Exhalation Retardation

FIGURE 3


EFFECT OF CPPB ON LUNG COMPLIANCE IN PULMONARY EDEMA
6.0
4.0
2.0
0
Lung Volume (L.)
CPPB
10
20
30
40
Pressure (cm H_2O)