MEDICAL GRAND ROUNDS, MAY 18, 1989

THE ADULT RESPIRATORY DISTRESS SYNDROME

"In the course of clinical and laboratory observations on 272 adult patients receiving respiratory support, a few patients did not respond to usual methods of therapy . . ."

Ashbaugh, D.G. Acute respiratory distress in adults. Lancet 2:319, 1967.

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INTRODUCTION

In 1967, Ashbaugh (1) described a group of twelve patients suffering from a severe form of respiratory failure, characterized by refractory hypoxemia, stiff lungs, and diffuse infiltrates on the chest radiograph. The patients had a variety of underlying illnesses, including trauma, pancreatitis, and pneumonia. Seven patients died and on postmortem examination extensive alveolar hemorrhage, edema, and intra-alveolar hyaline membranes were present. The authors named the condition the Acute Respiratory Distress Syndrome of Adults and postulated that it was produced by a common mechanism. In 1971 the same investigators renamed the syndrome the Adult Respiratory Distress Syndrome, or ARDS. ARDS is estimated to affect 150,000 people/year in the United States and is a common cause of admission to an intensive care unit. Despite a great deal of investigation into the mechanisms of ARDS, little therapeutic progress has been made and mortality remains high. This presentation will review the clinical features, pathophysiology, pathogenesis, and therapy of ARDS. Special emphasis will be placed on the role played by the polymorphonuclear leukocyte (PMN) in initiating ARDS.

DIAGNOSIS OF ARDS

TABLE 1

DIAGNOSTIC CRITERIA FOR ARDS

1. CLINICAL - Acute onset of respiratory distress in a patient with a predisposing condition
2. RADIOGRAPHIC - Diffuse infiltrates on chest x-ray
3. PHYSIOLOGIC
   a. $PaO_2 < 50$ mmHg with an $FIO_2 > 60\%$
   b. Total respiratory compliance < 50 ml/cmH_2O
   c. Normal left atrial pressure (PCWP $\leq$ 12 mmHg)

Table 1 lists the five criteria which should be met to make a secure diagnosis of ARDS. Dyspnea usually occurs suddenly and typically progresses over hours to overt respiratory failure, requiring endotracheal intubation and mechanical ventilation. Most patients have one or more of the predisposing conditions shown on Table 2, which is an extensive list of all the afflictions associated with ARDS. The four conditions marked with an asterisk - trauma, sepsis, gastric aspiration, and nosocomial pneumonia - precede more than 50% of ARDS cases. No

causal relationship to ARDS should be inferred from this list, and for some of the listed conditions the relationship is tenuous. For example, hypovolemic shock occurring without trauma is rarely followed by ARDS (2).

TABLE 2

CONDITIONS ASSOCIATED WITH THE ADULT RESPIRATORY DISTRESS SYNDROME

* Trauma	Air Embolism
* Sepsis	Granulocytic Leukemia
* Gastric Aspiration	Drugs (Heroin, Methadone,
* Nosocomial Pneumonia	Acetylsalicylic Acid)
Hypovolemic Shock	Paraquat
Multiple Transfusions	Smoke Inhalation
Burns	Oxygen Toxicity
Pulmonary Contusion	Disseminated Intravascular
Near Drowning	Coagulation
Cardiopulmonary Bypass	Miliary Tuberculosis
Fat Embolism	Ionizing Radiation
Pancreatitis	Viral, Mycoplasma,
	Pneumocystis Pneumonia

* Common

The chest radiograph of ARDS patients shows diffuse opacification due to accumulation of edema fluid in the lung parenchyma. An interstitial pattern is present early, but rapid evolution into an alveolar pattern of homogeneous and confluent infiltrates, produced by edema fluid flooding into alveolar spaces, is common. The radiographic pattern of pulmonary edema per se is nonspecific and cannot be distinguished from pulmonary edema due to left ventricular failure. However, ancillary findings are often present on the radiograph which help in distinguishing cardiogenic edema from ARDS (Table 3).

TABLE 3

RADIOGRAPHIC FEATURES OF CARDIOGENIC PULMONARY EDEMA AND ARDS

FEATURE	CARDIOGENIC	ARDS
Heart size	Enlarged	Normal
Pulmonary vasculature	Cephalized	Normal
Peribronchial cuffs	Common	Absent
Air bronchograms	Absent	Common
Edema distribution	Central	Peripheral
Pleural Effusions	Common	Absent

The physiologic measurements used to diagnose ARDS include severe hypoxemia, defined as a PaO_2 < 50 mmHg while the patient is breathing more than 60% oxygen. This degree of hypoxemia is produced by the presence of large areas of lung which are perfused but not ventilated, and the blood flow to unventilated lung is considered an intrapulmonary shunt. In ARDS, the proportion of shunt flow is usually 30% or more (i.e. $QS/QT \geq 30\%$ QS=shunt flow, QT=total pulmonary blood flow). Hypoxemia due to shunting is characteristically unaffected by increases in the FIO_2. The extensive pulmonary edema of ARDS causes the lungs to become stiff and noncompliant, which greatly increases the work of breathing and causes tachypnea. The compliance of the total respiratory system (lungs, chest wall, and diaphragm) can be measured by occluding the mechanical ventilators' expiratory circuit at the end of a tidal volume inspiration and reading the pressure on the ventilators' manometer;

$$\text{Total Respiratory Compliance} = \frac{\text{Tidal volume (ml)}}{\text{Manometer Pressure (CM } H_2O)}$$

If positive end expiratory pressure (PEEP) is being used, the amount of PEEP should be subtracted from the manometer pressure. Normal compliance values are 90-110 ml/CMH_2O, and in ARDS compliance is typically < 30 ml/CMH_2O. The final diagnostic criteria is a pulmonary capillary wedge pressure (PCWP) $\leq$ 12mmHg. Accurate clinical estimation of the PCWP is exceedingly difficult in critically ill patients, and even experienced clinicians correctly predict the PCWP only 50% of the time (3,4). Futhermore, fulminant cardiogenic edema results in similar radiologic and physiologic findings as ARDS. Thus, most investigators recommend that a diagnostic right heart catheterization, with measurement of the PCWP, be performed soon after ARDS onset.

RISK OF DEVELOPING ARDS

Two studies have recently been reported which quantify the risk of developing ARDS for hospitalized patients. Both studies indentified all patients in their institutions with ARDS risk factors and prospectively followed them. The diagnosis of ARDS was made only if all of the diagnostic criteria shown on Table 1 were met. The study by Fowler et al (5) involved three large hospitals over a 1 year period, and 993 patients with the risk factors shown (Table 4) were identified. The Pepe study (6) was performed at one hospital and enrolled only endotracheally intubated patients.

TABLE 4

ARDS INCIDENCE IN AT RISK PATIENTS

	Fowler (5)		Pepe (6)	
	#ARDS/#Risk	%ARDS	#ARDS/#Risk	%ARDS
Sepsis	9/239	4	5/13	38
Gastric Aspiration	16/45	36	7/23	30
Fracture	2/38	5	1/12	8
Multiple Transfusions	9/197	5	4/17	24
Cardiac Bypass	4/237	2	--	--
DIC	2/9	22	--	--
Nosocomial Pneumonia	10/84	12	--	--
Pulmonary Contusion	--	--	5/29	17
Near Drowning	--	--	2/3	66
Pancreatitis	--	--	1/1	100
Hypotension	--	--	0/1	0
Single Risk Factor	54/936	6	25/99	25
Multiple Risk Factors	14/57	25	24/37	65

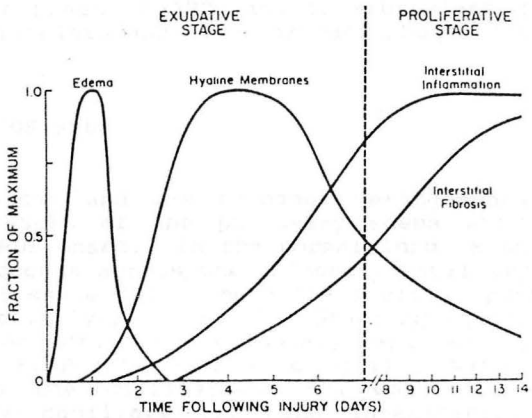
The ARDS incidence rates in the Fowler Study varied from 2% (bypass, burns) to 36% (gastric aspiration), with higher incidence rates for sepsis (38%), fracture (8%), and transfusions (24%) in the Pepe study. The higher rates in the latter study may be due to the fact that all patients were intubated, and presumably sicker. The Pepe study defined sepsis as hypotension with a low systemic vascular resistance and a "clinical picture" of a serious bacterial infection; positive blood cultures were not required and, of the six culture negative sepsis patients, three (50%) developed ARDS. Both investigators noted that the risk factors they used to identify at risk patients correctly identified 80% of all patients developing ARDS during the study period. A synergistic effect of multiple risk factors on incidence was found by both groups, as shown on the last two rows of Table 4. A final piece of important clinical data from both investigations was that ARDS usually (>80%) develops within 48 hours of a risk factor. Thus, patients surviving for 2 days after a risk factor event will usually not develop ARDS.

PATHOLOGY

Despite the wide variety of conditions associated with ARDS, the morphologic changes in the lung are similar and follow a stereotypic course. The term diffuse alveolar damage (DAD) describes the pathologic findings, and DAD is divided into an acute (exudative) stage and a chronic (organizing or proliferative) state (Figure 1) (7).

FIGURE 1.

The Exudative and Proliferative Stages of Diffuse Alveolar Damage (DAD)



Katzenstein, A. Surgical Pathology of Non-Neoplastic Lung Disease. W.R. Saunders, 1982.

The changes of acute DAD, present from Day 1 to Day 7, include a marked loss of endothelial and type 1 alveolar epithelial cells. A hemorrhagic edema is present in the interstitial and alveolar spaces and thick hyaline membranes, composed of fibrin and cellular debris, line the alveoli. PMNs are present throughout and morphometric studies have confirmed an eight fold increase in the number of PMNs (8-11). Diffuse thrombosis of small (<1mm diameter) and large pulmonary arteries is common, with thrombi composed of fibrin, PMNs, and red blood cells (12). Prominent accumulation of platelets is unusual.

The proliferative stage begins after Day 7. A marked hyperplasia of Type II alveolar epithelial cells occurs as the

cells attempt to restore an epithelial surface over denuded basement membrane exposed by the loss of Type 1 cells. Proliferation of fibroblasts occurs in both the interstitial and alveolar spaces, and histologic evidence of fibrosis begins to appear approximately seven days after ARDS onset. Some investigators have found an increased collagen content in the lungs of all patients dying after 10 days of ARDS (13), whereas others have found that only 1/3 of such patients have increased collagen (14). Fibrosis may proceed very rapidly, leaving the patient with an end stage "Honeycomb" lung within weeks. The presence of extensive fibrosis on lung biopsy is a poor prognostic finding and is associated with an 80% mortality rate (15). At the present time our understanding of the factors causing fibroblast proliferation in ARDS is minimal, although it is likely that fibroblasts are responding to chemotactic factors (fibronectin fragments, elastin peptides, and LTB_4) released during the acute phase of ARDS and to fibroblast growth factors released from platelets and alveolar macrophages (16-20).

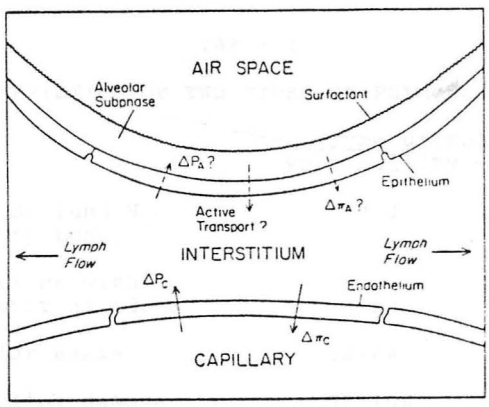
PATHOPHYSIOLOGY OF ARDS

The mechanical and gas exchange derangements occuring in ARDS are the result of the pulmonary edema which accumulates shortly after ARDS onset. In the normal lung, a net movement of 20 ml fluid/hr occurs across the pulmonary capillary bed and into the interstitial space (21), where the fluid is promptly removed by the interstitial lymphatics. The Starling equation represents the forces acting across the pulmonary capillaries, as shown by the formula $Qf=K[(Pc-Pi) - r(\pi c - \pi i)]$, with Qf=net fluid movement across the capillaries, K=a constant, P=hydrostatic pressure in the capillary (Pc) and interstitium (Pi), r=the reflection coefficient (a measure of capillary permeability), and π = the oncotic pressure in the vessels (πc) and interstitium (πi). Normally, r is close to one and the main factor determining fluid movement into the interstitial space is the pulmonary capillary hydrostatic pressure (22).

Pulmonary edema can be classified according to underlying mechanism (high pressure or cardiogenic versus high permeability edema) or by the anatomic site(s) involved (interstitial versus alveolar edema). To understand the pathogenesis of edema formation in ARDS, it is helpful to consider the lung as being composed of two discrete compartments, the interstitial and the alveolar space (Figure 2). The interstitial space is defined by the capillary endothelium and alveolar epithelium. Morphologic studies (23,24) have shown small (40Å) slits between endothelial cells, while alveolar epithelial cells are joined together by tight junctions (zonulae occludens). Functional studies have demonstrated that small molecules (<40,000 daltons molecular weight) can pass through the normal endothelial barrier, but alveolar epithelium is normally completely impermeable and blocks

even the passage of electrolytes. This relative endothelial leakiness accounts for the normal movement of fluid and protein into the interstitial space. The impermeability of the alveolar epithelium prevents any entry of fluid from the interstitium into the alveoli, thus preserving the gas exchange function of the lung.

FIGURE 2



Annals Int. Med. 99:814, 1983.

Cardiogenic edema occurs due to an increase in the capillary hydrostatic pressure; endothelial permeability remains low and there is a net movement of water, but not large molecular weight proteins, into the interstitial space. Three factors act to limit the effect of cardiogenic edema on pulmonary function (22). First, lymph flow rates increase up to ten fold. Second, the increased amount of interstitial water dilutes the interstitial protein concentration, which decreases interstitial oncotic pressure and opposes further entry of water into the lung. Lastly, the alveolar epithelial barrier remains impermeable, excluding edema from the alveolar space and preserving gas exchange. Although alveolar edema does occur during severe heart failure, the fluid enters the alveoli by passing through the bronchiolar epithelium and spilling into the alveoli in a retrograde fashion. As a result of these protective mechanisms, hypoxemia due to cardiogenic edema is usually mild and responds readily to low concentrations of inspired oxygen.

The edema of ARDS results from an injury which increases the permeability of both the endothelial and alveolar epithelial cells. The increase in epithelial cell permeability allows protein rich edema fluid to move from the interstitial space, where lymphatic drainage can remove it, and into the alveolar space, where clearance is less efficient (25). Thus, a

consistent finding in lung specimens of patients dying early in the course of ARDS is a large amount of alveolar edema (10), and disruption of tight alveolar epithelial cell junctions has been shown in a canine ARDS model (26,27). Animal experiments comparing high pressure and permeability edema have demonstrated marked differences in the distribution of edema (Table 6).

TABLE 6

CHARACTERISTICS OF TWO TYPES OF PULMONARY EDEMA

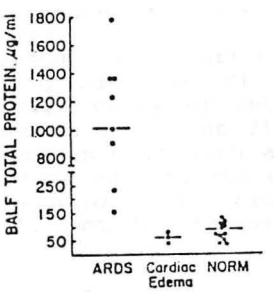
	Type of Pulmonary Edema	
	Permeability	High Pressure
Extravascular lung H_2O (GrH_2O/Gr Dry Lung)	8.2	8.2
# Lung Sections with:		
Interstitial edema	9/64	21/60
Alveolar edema	52/64	18/60
Epithelial damage	31/108	1/25
Intrapulmonary Shunt (%)	48	39

JCI 77:1786, 1986

For equal amounts of total lung water, permeability edema predominantly involved the alveolar space and was associated with more alveolar epithelial damage and a larger shunt.

Investigation of ARDS pulmonary edema in humans has been performed by utilizing bronchoalveolar lavage (BAL) to obtain alveolar edema fluid. Such studies have demonstrated the rapid accumulation of radiolabeled albumin from the blood into the alveolar space of ARDS patients, compared to patients with cardiogenic edema (28). Measurement of the protein content of edema has been suggested as a diagnostic test for distinguishing cardiogenic and permeability edema (Figure 3) (29,30). Not only is the amount of protein increased in ARDS, but very large molecules, such as IgM (900 Kd), appear in ARDS BAL samples (31). The appearance of such large plasma proteins is indicative of the severe epithelial cell damage which occurs in ARDS.

FIGURE 3



JCI 78:1517, 1989

TABLE 7

PHYSIOLOGIC CONSEQUENCES OF ALVEOLAR EDEMA IN ARDS

Decreased vital capacity and functional residual capacity ⟶ airway closure

Decreased compliance ⟶ increased work of breathing

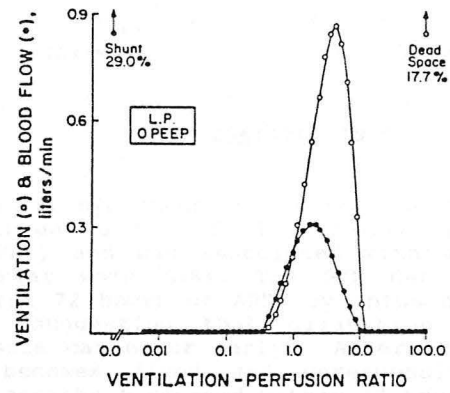
Intra pulmonary shunt of blood flow to unventilated alveoli ⟶ refractory hypoxemia

The physiologic consequences of lung edema in ARDS are listed on Table 7. A fall in the functional residual capacity is uniformly present and contributes to ventilation perfusion inequality by causing air trapping distal to areas of airway closure (32). Defective surfactant may be partially responsible for the small lung volumes, as BAL studies have detected decreases in the lecithin/sphingomyelin ratio, % of disaturated lecithin, and complete absence of surface tension lowering activity in surfactant material obtained from ARDS patients (33,34). The biochemical abnormalities of ARDS surfactant resemble those present in premature neonates with hyaline membrane disease. Loss of surfactant activity might act to worsen edema accumulation in ARDS, as increases in alveolar surface tension have been shown to increase lung water content by lowering interstitial hydrostatic pressure (35). A decrease in lung compliance occurs due to the increased recoil pressure of the edematous lung, which increases the work of breathing and leads to respiratory muscle fatigue.

The most serious and life threatening derangement of ARDS is the presence of large areas of totally unventilated lung. Dantzker (36) has quantitated, using an inert gas technique, the amount of pulmonary blood flow perfusing unventilated lung (intrapulmonary shunt; V/Q ratio of 0) in ARDS patients; the results of a representative study of one patient are shown in Figure 4. A mean intrapulmonary shunt flow of 38% was found in 16 ARDS patients. The presence of such a large amount of shunt flow explains the difficulty encountered clinically in achieving adequate arterial oxygenation, as blood perfusing totally unventilated alveoli will not become oxygenated even if 100% oxygen is inhaled (37).

FIGURE 4

Distribution of Ventilation and Perfusion in a Patient with ARDS

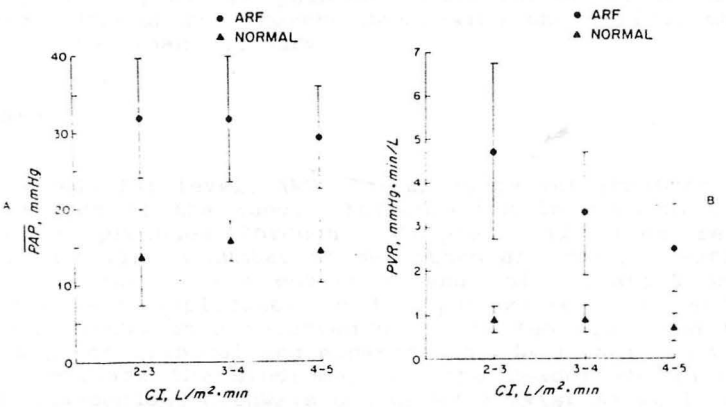


ARRD 120:1045, 1979

The pulmonary vasculature is prominently affected by ARDS. Right heart catheterization performed on thirty ARDS patients revealed pulmonary hypertension (mean pulmonary artery pressure >25 mmHg) in all (Figure 5).

FIGURE 5

MEAN PULMONARY ARTERY PRESSURES (PAP) AND PULMONARY VASCULAR RESISTANCE (PVR) IN 30 PATIENTS WITH ARDS



NEJM 296:476, 1979

The pulmonary hypertension was not due to hypoxemia and was caused by a three to five fold increase in pulmonary vascular resistance (PVR), and was associated with a large increase in right ventricular work (38). The PVR can usually be lowered during the first 72 hours of ARDS by infusing nitroprusside or isoproterenol, suggesting that dilatation or recruitment of pulmonary vessels can occur early. After 72 hours the elevated PVR usually becomes fixed and unresponsive to drugs (39). Pulmonary angiography performed within 48 hours of ARDS onset has shown that 48% of patients have demonstrable filling defects in vessels of >1mm diameter (40), and intravascular thrombi, composed of fibrin and PMNs, and a decreased number of >1mm diameter pulmonary arteries are commonly found at autopsy (41). The reversibility of the early pulmonary hypertension suggests that vasoactive inflammatory mediators may be involved, and the fixed nature of late pulmonary hypertension is probably due to in situ thrombosis and fibrosis occluding the vascular bed.

Vascular involvement may also be an important determinant of ARDS outcome. Pulmonary hypertension worsens pulmonary edema by increasing capillary hydrostatic pressure and by increasing the effective pore size of pulmonary endothelial cells (42). A decrease in the PVR commonly occurs several days after ARDS onset in survivors, while non-survivors tend to have a persistently

elevated PVR (39). The permeability surface area for urea (PSU), a measurement of pulmonary blood flow perfusing "leaky" capillaries, has been determined in ARDS patients and related to outcome. ARDS survivors and non-survivors had identical amounts of lung water, but survivors had a significantly lower PSU, and PSU correlated well with the alveolar-arterial O_2 gradient (43). Thus, the ability of the pulmonary circulation to decrease flow to injured lung units, thereby decreasing shunt flow, may be an important determinant of survival.

PATHOGENESIS

On a cellular level, ARDS is an acute inflammatory reaction involving much of the lung. Inflammation in vivo is a complex event which procedes through multiple, and often redundant, pathways involving a number of mediators and cells. Rather than attempt a review of the entire melange of mediators and cells which have been implicated in the pathogenesis of ARDS, this review will focus on a selected group of mediators and the PMN. A large body of clinical and experimental data indicate that PMNs commonly initiate the syndrome, but the reader should be aware that PMN independant pathways undoubtedly exist as well (44).

Inflammatory Mediators Initiating ARDS

Bacterial lipopolysaccharide (LPS),tumor necrosis factor (TNF), and complement are three inflammatory mediators for which there is convincing clinical and/or experimental evidence suggesting an important role in ARDS. Although the effects of these mediators on PMNs will be emphasized, both LPS and TNF have direct effects on endothelial cells which may be important. Conditions such as sepsis and trauma affect the lung by releasing mediators into the systemic circulation, whereas nosocomial pnumonia, gastric aspiration, and other pulmonary diseases cause local production of mediators. Although they will not be reviewed, it is possible that a role in the initiation and/or perpetuation of ARDS will be demonstrated for platelet activating factor (45,46), interleukin 1 (47), and leukotrienes (48-50).

1. Lipopolysaccharide (LPS). Nanogram/ml (ng/ml) concentrations of LPS are detectable in the blood of patients with gram negative bacteremia (51) and, although many of the manifestations of septic shock are mediated by TNF (vide infra), LPS has a number of important pro-inflammatory direct effects. Low concentrations (ng/ml) of LPS increase PMN adherence to endothelial cells (52), and leukopenia developing in rabbits after LPS infusion is not TNF dependent (53). LPS primes PMNs for augmented O_2^- release when a second stimulus is delivered (54). Endothelial cells exposed to LPS for brief periods develop increased adhesiveness for PMNs (55), release a PMN chemotactic factor (56), and express tissue factor activity capable of initiating blood

coagulation via the extrinsic pathway (57). Prolonged (24 hr) LPS exposure is toxic to endothelial cells and increases endothelial monolayer permeability (58,59). LPS interacts with the complement system by generating phlogistic complement products via activation of the alternative complement pathway (60). Since gram negative bacteremia frequently precedes ARDS, these direct LPS effects may be important in initiating pulmonary injury.

2. Tumor Necrosis Factor (TNF). TNF is a potent cytokine which is rapidly (within 90 minutes) released in large amounts by macrophages exposed to LPS or viruses (61). Table 8 summarizes the inflammatory effects of TNF.

TABLE 8

Inflammatory Effects of TNF

In Vivo

- Fatal shock with pulmonary edema, renal failure
- Pulmonary PMN sequestration, leukopenia, high permeability pulmonary edema

In Vitro

- Increased PMN O_2^- release, adherence, lysosomal enzyme release
- Increased endothelial cell adhesiveness for PMNS
- Endothelial cell injury

Infusion of gram negative bacteria or LPS into primates (62,63) produces septic shock, which can be prevented by pretreatment with anti-TNF antibody. Microgram doses of recombinant TNF given to rats also produces lethal shock, and pulmonary edena with large numbers of PMNs have been noted in the animals lungs (64). TNF administered to dogs causes hypoxemia, leukopenia,and pulmonary hemorrhage (65). In vitro, ng/ml concentrations of TNF activate PMNs, via high affinity TNF receptors (66), and cause O_2^- and lysosomal enzyme release (67), and increased PMN adherence to endothelial cells (68). TNF causes endothelial cells to express tissue factor (69) and release Interleukin 1 (IL-1) (70), and an effect of TNF on endothelial cells promotes PMN adherence and migration across endothelial monolayers (71). Prolonged TNF exposure causes disruption of endothelial monolayers and loss of endothelial cell fibronectin (72).

Administration of small amounts of TNF, insufficient to cause fatal shock, have been shown to cause high permeability pulmonary edema in guinea pigs. Leukopenia, hypoxemia, and large numbers of PMNs were present in the lungs of TNF treated animals. Interestingly, no evidence of injury was noted in non-pulmonary organs, suggesting that the lungs may be especially susceptible to TNF induced injury (73). Administration of 4 ng/kg LPS to humans results in a rapid rise in plasma TNF and leukopenia (74), and an association between mortality, leukopenia, and circulating TNF levels has been noted in patients with meningococcemia (75). It is likely that future investigations in humans will demonstrate a role for TNF in sepsis associated ARDS (76,77).

3. Complement. Sepsis and trauma (78,79) are two conditions commonly associated with ARDS in which complement activation frequently occurs. C5a des arg, a complement activation product, is a potent PMN chemotaxin which also induces PMN adherence, O_2^- release, and lysosomal enzyme release (80). A prospective study of 61 patients at risk for ARDS reported increased C5a levels prior to ARDS onset in 31 of 33 patients developing ARDS; only 5 of the 28 patients not developing ARDS had elevated C5a (81). However, three other studies of similar groups of at risk patients have found that elevated C5a levels commonly occur in many seriously ill patients and do not predict ARDS (82-84). A recent investigation of 87 septic patients reported elevated levels of the terminal complement complex (C5a-C9) in the plasma of most patients prior to the onset of ARDS, and the levels remained elevated until ARDS resolved. The authors noted that the terminal complex was more stable than C5a and may be a better index of ongoing complement activation. (85).

Experiments in animals have shown that intra-tracheal administration of C5a or C5 induces high permeability pulmonary edema and an influx of PMNs (86). However, intravascular complement activation (87), or infusion of ex vivo C5a activated PMNs (88), produces pulmonary PMN sequestration without injury. Intravascular generation of C5a, following hemodialysis with cellophane membranes, has been described in humans (89). During dialysis patients developed leukopenia, increased C5a levels, and hypoxemia, but pulmonary edema did not occur (90). Thus, it appears that systemic complement activation alone is insufficient to cause ARDS. Experiments in rabbits have shown that infusion of C5a and LPS, but not either substance alone, causes pulmonary edema (91). Similar results were obtained with C5a and a brief (10 minute) exposure to hypoxia (92). The effect of hypoxia was blocked by pretreatment with a cyclooxygenase inhibitor, suggesting that hypoxia caused release of a prostaglandin mediator (92). Thus, it is likely that in humans, the effect of systemic complement activation may be

additive to that of other inflammatory mediators in producing ARDS.

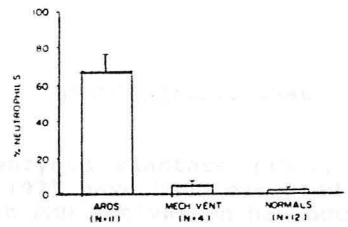
PMS and ARDS

The normal human lung contains a large number of PMNs in the pulmonary capillaries. These marginated cells are loosely adherent, easily mobilized by epinephrine, and rarely enter the lung parenchyma (94). In rabbits, the size of the pulmonary PMN pool varies inversely with blood flow (95), and if a similar relationship exists in humans, then shock would lead to large increases in the number of marginated pulmonary PMNs.

Clinical studies, as well as the pathologic studies reviewed earlier, suggest that PMNs enter the lung early in ARDS. Percutaneous lung biopsies have been performed on patients within hours of trauma and hypovolemic shock, and the biopsies from patients who later developed ARDS showed prominent PMN accumulation in pulmonary capillaries, with evidence of lysosomal granule release and endothelial injury (96). Three investigators have performed BAL within 24 hours of ARDS onset, and from 68 to 82% of the lavaged cells were PMNs; increased numbers of PMNs were not present in BAL obtained from intubated patients with non-ARDS respiratory failure (Figure 6) (97-99).

FIGURE 6

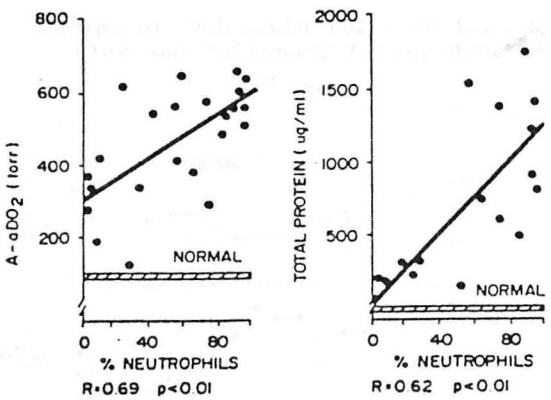
% PMN in BAL Fluid
Obtained Early in ARDS



ARRD 133:221, 1986

BAL has also been performed on 12 patients judged to be at high risk for ARDS, and a marked increase in PMNs was found in the 5 patients who subsequently developed ARDS (100). In patients with established ARDS, the % PMNs in the BAL fluid correlates well with both the alveolar to arterial (A-a) O_2 gradient and the BAL protein content (Figure 7) (97).

FIGURE 7
Correlation of the Alveolar-arterial (A-a) O_2 Gradient (A) and BAL Protein Content (B) with the % PMNs in BAL



ARRD 133:221, 1986

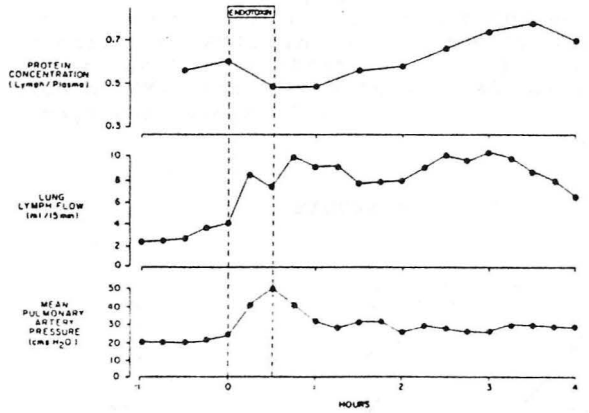
The PMN lysosomal enzymes elastase (101), collagenase (97,99), and myeloperoxidase (97) have been detected in ARDS BAL fluid as well, suggesting that PMN activation had occurred. An increase in the A-a O_2 gradient, from a group mean of 148 to 290 mmHg, and the onset of dyspnea has been observed in leukopenic (< 1,000 WBC/mm^3) patients during resolution of the leukopenia (102). Finally, a factor chemotactic for PMNs was found in BAL fluid in the majority (13/16) of patients lavaged within 24 hours of ARDS onset (98).

Although the findings noted in clinical studies suggest an association between ARDS and PMNs, they do not allow one to determine if PMNs are causing lung injury. Investigations suggesting a causal role for PMNs have been performed in several animal models, with the sheep model being the most relevant to human ARDS. Collection of pure sheep lung lymph is possible because the lung lymphatic vessels drain exclusively into a large caudal mediastinal node, which can be cannulated (103).

Chronically instrumented sheep can be studied in an unanesthetized state, with measurement of lung lymph flow, lymph protein content, lung mechanics, and hemodynamics. As a model for the pulmonary effects of gram negative bacteremia the instrumented sheep were originally given infusions of live Pseudomonas aeruginosa, but the animals frequently developed florid pulmonary edema and died (104). Subsequently, intravenous infusion of sublethal (<1ug/kg) doses of LPS were used, with better results.

FIGURE 8

Effect of Endotoxin (LPS) on Lung Lymph Flow and Pulmonary Artery Pressure



Lab. Invest. 48:460, 1983

Representative data from an experiment using the sheep model are shown on Figure 8, and the experimental results can be summarized as follows:

1. The pulmonary artery pressure rapidly increases during LPS infusion and then falls over 1-2 hours.

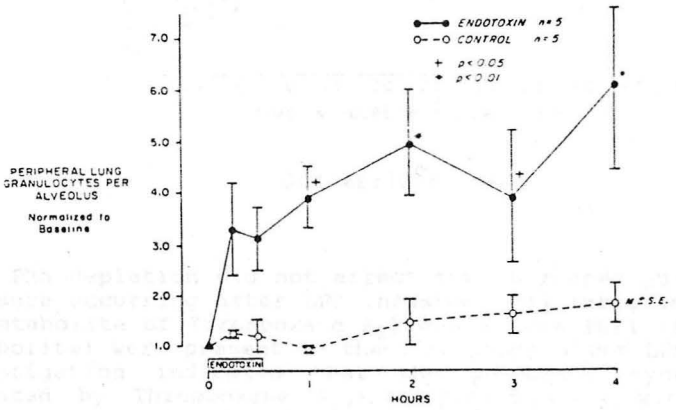
2. Lung lymph flow increases during LPS infusion and continues to increase for several hours. The protein content of the lung lymph also rises, producing a large increase in lung lymph protein clearance (lymph flow x lymph protein content) (105).

3. The increase in lung lymph protein clearance represented an increase in endothelial permeability, because the left atrial pressures remained constant and increased lymph protein clearance occurred even when the rise in pulmonary artery pressure was prevented. In contrast, inflation of a left atrial balloon in the animals caused a marked rise in left atrial pressure, increased lung lymph flow, but decreased the lung lymph protein content.

4. A marked drop in the number of circulating WBCs was noted ($9,634/mm^3$ to $1,900/mm^3$ 1 hr after LPS), at the same time that many PMNs were accumulating in the lungs (Figure 9). A high degree of correlation was noted between the fall in the peripheral WBC count and an increase in the A-a O_2 gradient (106).

5. Histologic examination of the lungs revealed accumulation and degranulation of PMNs in the pulmonary capillaries within minutes of LPS administration. Within 2 hours of LPS, migration of PMNs into the interstitial space and endothelial cell damage was evident (107).

FIGURE 9



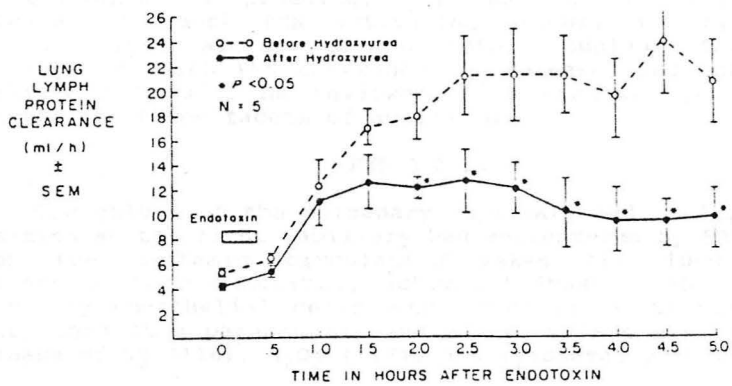
Lab. Invest. 48:462, 1983

Results similar to those noted above were obtained when zymosan activated plasma, a source of activated complement, was administered to sheep instead of LPS (108). PMN depletion by hydroxyurea pretreatment ablated the increase in lymph flow and

lymph protein clearance after LPS (Figure 10), suggesting that PMNs were necessary for increased endothelial permeability (109,110). Methylprednisolone, given 30 minutes prior to LPS and continued for 3 hours, prevented the increase in lung lymph protein clearance. However, methylprednisolone had no effect when given after lung lymph protein clearance had increased (111) The results from this sheep model of gram negative sepsis strongly support a central role for PMNs in producing the high permeability pulmonary edema characteristic of ARDS.

FIGURE 10

Effect of PMN Depletion on Lung Lymph Protein Clearance



JCI 68:1256, 1981

PMN depletion did not affect the increased pulmonary artery pressure occurring after LPS infusion, and large amounts of TxB_2 (a metabolite of Thromboxane A_2) and 6 keto PGF1 (a prostacyclin metabolite) were present in the lung lymph after LPS. Subsequent investigation indicated that the pulmonary hypertension was mediated by Thromboxane A_2, as pretreatment with a specific Thromboxane synthetase inhibitor (VK37-248) prevented both the rise in lung lymph TxB_2 and the increased pulmonary artery pressure (112,113). An additional vasoactive effect of prostaglandins, with prostaglandins acting as inhibitors of the normal hypoxic pulmonary vasoconstriction response, has been reported (114). Dogs infused with LPS had marked increases in circulating prostacyclin and thromboxane levels and a complete loss of pulmonary vasoconstriction in response to alveolar

hypoxia. Pretreatment with cyclooxygenase inhibitors restored hypoxic vasoconstriction. Since the effect of hypoxic vasoconstriction is to decrease perfusion to unventilated alveoli, prostaglandins may be involved in producing both the pulmonary hypertension and the large intrapulmonary shunt which are characteristic of ARDS.

Mechanisms of Lung Injury in ARDS

The presence of large numbers of PMNs is not injurious to the normal lung in vivo, and PMN activation must occur as an initial step in the genesis of PMN mediated pulmonary injury. Bacteria, immune complexes, LPS, TNF, FMLP (a peptide released from gram negative bacteria and mitochondria), and C5a all activate PMNs. Activation is defined functionally as increased PMN adherence and spreading, O_2^- production, and lysosomal enzyme release, and most PMN activating stimuli act by increasing cytosolic free calcium via a G protein coupled mechanism (115). The ways in which PMN adherence, O_2^- release, and enzyme release initiate ARDS will be reviewed, with emphasis on interactions between the three facets of activation.

PMN Adhesion

The volumn of the pulmonary capillary bed is large, and its position as the first capillary bed encountered by PMNs returning from the systemic circulation makes the lung especially vulnerable to accumulating activated PMNs. PMN adherence to pulmonary endothelial cells must occur prior to diapedesis and entry into lung parenchyma, and adherent PMNs exhibit augmented release of O_2^- (116), H_2O_2 (117), and lysosomal enzymes (118).

Recently, the molecular basis of PMN adherence has been elucidated. In 1980, Crowley (119) described a missing surface protein on PMNs obtained from children afflicted with recurrent bacterial infections. Affected children had persistent neutrophila, with 5-20 fold increased circulating PMN counts, and a striking absence of PMNs in infected tissue sites (120). In vitro, the PMNs adhered poorly to a variety of surfaces and had lessened chemotactic responses. The missing PMN protein has been identified as the CDw18 adhesion complex, which is a heterodimer composed of an α and B subunit (121). Normal resting PMNs have small amounts of CDw18 on their surface. Stimuli such as C5a, FMLP, TNF, and LPS induce a rapid (within minutes) 4-8 fold increase in the amount of cell surface CDw18; such rapid expression is possible because CDw18 is stored preformed in PMN secondary granules (122,123). Increased PMN CDw18 levels correlate with increased PMN adherence to endothelial cells and connective tissue matrices (124), and PMN adherence can be completely ablated by monoclonal anti-CDw18 antibodies (125). It has been suggested that PMN activation, in addition to causing quantitative increases in CDw18, also causes functional changes in the CDw18 complex which enhance adherence (126).

The leukopenia and pulmonary dysfunction of hemodialysis patients which was earlier reviewed was associated with increased PMN CDw18 levels (127). Direct measurment of CDw18 on PMNs from patients at risk for ARDS, or with established ARDS, has not been reported. However, there is evidence suggesting that circulating PMNs from ARDS patients are activated. PMNs from patients with early ARDS produce more O_2^- and have increased chemotaxis in vitro (128). A prospective study of 40 patients with ARDS risk factors investigated the relationship between the circulating WBC count and ARDS (Table 9). 80% of patients developing ARDS had a fall in their WBC count, usually in the 24 hour period prior to ARDS onset (129).

TABLE 9

Relationship Between Leukopenia and the Development of ARDS

WBC Count	+ ARDS	- ARDS
	(No. of patients)	
$<4,200/mm^3$	8	4
$>4,200/mm^3$	2	26

Presumably, the leukopenia was due to PMNs accumulating in the lung. In vitro, anti-CDw18 antibodies have been effective in preventing lung injury in an animal ARDS model (130) and have prevented PMA stimulated PMNs from damaging alveolar epithelial cells (131). Anti CDw18 antibodies could prevent PMNs from damaging pulmonary capillary endothelial cells and from entering the interstitial space, and therapy with such antibodies has potential for preventing ARDS.

PMN-Endothelial Cell Interaction

Little attention has been given thus far to the pulmonary endothelium where ARDS begins. Although endothelial cells have long been thought of as passive participants in inflammation, it has become evident that they are metabolically active cells which respond to inflammatory mediators in a number of ways. For example, LPS and TNF stimulate fibrin formation on the endothelial surface by inducing endothelial cell tissue factor production (69), and LPS, TNF and IL-1 have been shown to induce synthesis and release of a 7.5 Kd PMN chemotactic factor from cultured human endothelium (56).

Endothelial cells also interact with PMNs by expressing adhesion molecules; two such molecules have been identified to date and have been designated Intercellular Adhesion Molecule 1 (ICAM-1) and Endothelial Leukocyte Adhesion Molecule 1 (ELAM-1). ICAM-1 has been detected on human endothelial cells from multiple sites and is constitutively expressed (132,133). CDw18

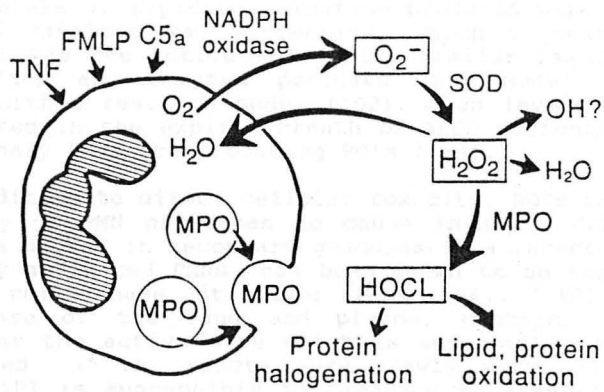
is thought to be the PMN surface structure recognizing and adhering to ICAM 1 (134). ELAM-1 is not expressed on normal endothelial cells, but exposure to LPS, TNF, or IL-1 causes rapid appearance of endothelial cell ELAM-1 resulting in increased PMN adherence which is independant of CDw18 (135). The amino terminal 120 amino acids of ELAM-1 resemble that of known animal lectins, and ELAM-1 is thought to recognize PMN cell membrane carbohydrates (136). In vivo, ELAM-1 expression has been demonstrated on endothelial cells from inflammatory sites (137). Thus, inflammatory stimuli present during ARDS can both increase PMN CDw18 levels and act directly on endothelial cells to promote PMN adherence by a CDw18 independent mechanism.

Reactive Oxygen Intermediates

Most stimuli which activate PMNs result in NAPDH oxidase activation, and NADPH oxidase catalyzes the formation of O_2^- from oxygen. The reactive oxygen intermediates (ROIs) produced from O_2^- are exceedingly damaging to proteins and cells and may be important in producing ARDS. This section will review investigations pertinent to the role of ROIs in inflammatory lung injury.

The pathways of O_2^- metabolism used by stimulated PMNs are outlined on Figure 11.

FIGURE 11.



O_2^- is rapidly reduced to H_2O_2 by superoxide dismutase. H_2O_2 is a stable ROI which can directly injure endothelial cells (138),

but little H_2O_2 is present in the medium of activated PMNs. Additionally, endothelial cells contain catalase and a glutathione peroxidase - glutathione reductase system capable of metabolizing H_2O_2 (139). The major pathway of H_2O_2 metabolism involves a myeloperoxidase catalysed reaction between H_2O_2 and any available halide (usually CL) to produce HOCL. Myeloperoxidase is released from activated PMNs and binding of myeloperoxidase, a highly basic protein, to target cell membranes has been demonstrated to markedly increase the cellular toxicity of HOCL (140). Approximately 40% of the H_2O_2 produced by activated PMNs forms extracellular HOCL (141). HOCL is an extremely reactive oxidizing agent which reacts with amino groups on proteins to produce chloramines, oxidizes sulfhydryl groups, and damages cell membranes by lipid peroxidation (142, 143).

A number of in vitro investigations have suggested that PMNs damage pulmonary endothelial and epithelial cells by HOCL production (144-147). However, these experiments were performed using serum and protein free solutions. HOCL is so reactive that even small amounts of plasma proteins act as HOCL scavengers, reacting with HOCL to produce chloramines (148). Thus, the presence of small amounts of serum protects cells from HOCL (138). The scavenging effect of plasma proteins is probably important in ARDS, since high protein concentrations are present in the interstitial and alveolar space.

The results of <u>in vivo</u> animal experiments suggest that ROIs can produce high permeability pulmonary edema. Intra-tracheal administration of the HOCL generating enzymes glucose oxidase and myeloperoxidase induced pulmonary edema in rats (149). Intravenous cobra venom factor, which causes massive complement activation, caused PMN mediated pulmonary edema in rats (150). Elevated levels of lipid peroxidation products were noted in the blood, and catalase was protective, which suggests that H_2O_2 and/or HOCL was the active ROI (151). Similar results have been obtained from an isolated perfused lung model (146) and a pulmonary Arthus reaction model (152). High levels of H_2O_2 have been detected in the expired breath of ARDS patients, suggesting that pulmonary PMNs are producing ROIs (153).

In addition to direct cellular toxicity, ROIs may potentiate the ability of PMN proteases to cause injury. PMNs contain a collagenase stored in secondary granules in a latent form. HOCL, produced by activated PMNs, has been shown to be responsible for activating collegenase outside of PMNs (154). α_1PI, the primary anti-elastase of the lung and plasma, contains a methionine residue near the active site which is susceptible to oxidation, and oxidized α_1PI reacts very slowly with elastase (155). Oxidized α_1PI is susceptible to cleavage by elastase (156). In vitro, 10^6 PMNs, the approximate number of PMNs in 1 ml of blood, can produce sufficient HOCL to inactive 300 ug α_1PI, but this represents only 25% of the α_1PI plasma concentration (1.2 mg α_1PI/ml). Additionally, presence of even small amounts of other proteins, such as albumin, scavenges HOCL and protects

α_1PI from oxidative inactivation (157). Investigations in humans have shown that oxidized α_1PI is present in ARDS BAL fluid (158,159). However, in most cases large amounts of active, unoxidized 1PI were present as well (160,162). Thus, a major problem with implicating HOCL as a mediator of ARDS lung injury is the high concentrations of plasma proteins in ARDS edema, as it is likely that any HOCL produced by PMNs would be scavenged by edema proteins before cellular injury could occur.

PMN Proteolytic Enzymes and ARDS

PMN lysosomal granules contain two enzymes - collagenase and elastase - active at a neutral pH. Oxidative activation of collagenase has been reviewed; collagenase activity has been detected in ARDS BAL (97), suggesting that collagenase may be involved in matrix degradation.

Elastase is a potent protease which is present in PMN primary granules and is released by phagocytosing or dying PMNs (163). Elastase is active against a variety of proteins and cells (Table 10).

TABLE 10

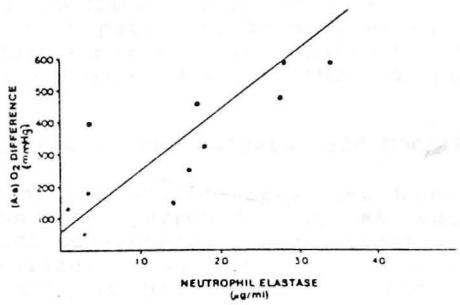
Effects of Elastase

- Elastin Degradation
- Types III and IV collagen degradation
- Fibronectin digestion
- Cell Injury

As is evident from Table 10, elastase is capable of destroying multiple components of lung interstitial matrix and basement membrane (164-166). In vitro, using serum free systems, PMN elastase causes increased endothelial monolayer permeability (167), endothelial cell detachment (168) and lysis (52), and alveolar Type II epithelial cell injury (130). Early investigations into the mechanisms of inflammatory injury during dermal Arthus reactions implicated PMN elastase in basement membrane destruction, edema formation, and endothelial cell necrosis (169-171). Elastin degradation products have been detected in serum and BAL from ARDS patients (172), and ARDS BAL fluid has been shown to contain a factor(s) capable of inducing PMN elastase release (173). Additionally, a correlation between antigenic elastase BAL concentrations and the A-a O_2 gradient has

been demonstrated, suggesting an association between elastase release and lung injury (Figure 12) (97).

FIGURE 12



ARRD 132:1103, 1985

Interest in elastase as an agent of acute pulmonary injury began in 1981, when Lee (101) detected elastase activity in ARDS BAL fluid. However, three subsequent investigators have not detected elastase activity in ARDS BAL, despite the presence of high levels of antigenic elastase (Table 11).

TABLE 11

Elastase, α_1PI Levels in ARDS BAL

			Elastase		α_1PI	
Author	Year	#Pts	Antigenic (% of Patients)	Functional	Antigenic (% of Patients)	Functional
Lee	1981	23	ND	44	100	54
McGuire	1982	24	ND	64	66	50
Idell	1985	13	100	0	100	ND
Weiland	1986	18	100	0	100	ND
Wewers	1988	7	71	0	100	100

The three investigators reporting no elastase activity all performed BAL with large volumes of saline, whereas the initial two studies which detected elastase activity used small volume lavage; large volume BAL samples the alveolar space of the lung

more accurately, and thus technical reasons may explain the discrepant results (174). A common finding of all studies was the presence of large amounts of protein, including α_1PI and α_2 macroglobulin, in BAL. The concentrations of α_1PI ranged from 10 to 40 fold above normal. Although a proportion of the α_1PI was oxidized and inactive, large amounts of active α_1PI were still present in most patients. Thus, free elastase activity is not present in the lungs of ARDS patients, and anti-elastase levels are actually augmented due to the high permeability edema.

PMN Adherence, Proteolysis, and HOCL Release

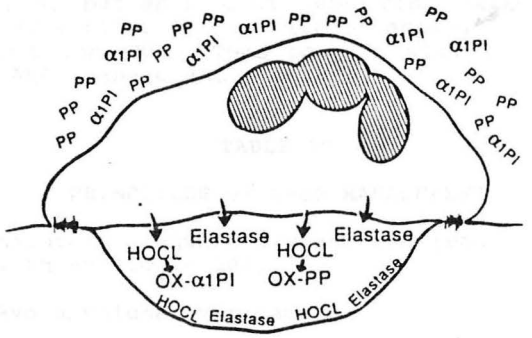
The results of the studies presented thus far suggest that during ARDS PMNs are surrounded by an excess of elastase inhibitors and HOCL scavengers, and any elastase or HOCL released is quickly neutralized. How, then, does the PMN initiate lung injury during ARDS? It has become apparent that adherence of PMNs to either cells or connective tissue matrices is critical for injury to occur. The initial observation stimulating interest in PMN adherence was made by Wright, who noted that phagocytosing macrophages were able to exclude proteins of >50 Kd molecular weight from the area of cell-matrix contact (175). Campbell (176) investigated the ability of stimulated PMNs to degrade a fibronectin matrix and found that large amounts (100 fold in excess of the PMNs total elastase content) of α_1PI were unable to block proteolysis. Catalase did not increase α_1PI efficacy, suggesting that oxidative inactivation of α_1PI by activated PMNs was not the reason for the persistent proteolysis. The same investigator later demonstrated that activated PMNs, in the presence of α_1PI, degraded matrix protein only in areas directly below the cells. Exclusion of α_1PI from the area of PMN-matrix contact was demonstrable (177). Subsequent investigators have confirmed these results and have shown that activated PMNs degrade matrix proteins even when 100% plasma, containing a 30,000 fold molar excess of α_1PI, is present (178). Although large molecular weight elastase inhibitors such as α_1PI and soy bean trypsin inhibitor were ineffectual, small molecular weight chloromethylketone elastase inhibitors (600 daltons) completely blocked PMN proteolysis (179).

Similar results have been obtained from investigations of PMN cytotoxicity. PMNs, stimulated with LPS and FMLP, adhered tightly to endothelial cells and lysed the cells even in the presence of 50% plasma or α_1PI, although a low molecular weight elastase inhibitor was protective. Stimulated PMNs from a chronic granulomatous disease patient, which do not produce ROIs, did not damage endothelial cells. The results of these experiments suggest that adherent PMNs utilize both proteases and ROIs to produce cellular injury (52). Harlan has demonstrated that FMLP stimulated PMNs, suspended in 10% serum, are capable of producing increased permeability of endothelial monolayers. PMNs from patients with chronic granulomatous disease or CDw18

deficiency were ineffective, suggesting that proteases and tight adherence are important in inducing capillary leaks (166).

Thus, it is likely that PMNs initiate ARDS by first becoming tightly adherent to pulmonary endothelial cells and basement membrane. The adherent, activated PMN is able to create a subcellular zone excluding the large amounts of surrounding plasma proteins (Figure 13).

FIGURE 13



PP = Plasma Protein α1PI = Protease inhibitor

Release of HOCL, elastase, and collagenase into the subcellular zone inactivates any protective proteins present and allows unimpeded proteolytic and HOCL activity on the underlying matrix or cell. This integrated PMN activation response effects inflammatory injury even when large amounts of inhibitors are present in the surrounding inflammatory milieu.

ARDS in Neutropenic Patients

Although this review has emphasized the PMNs role in producing ARDS, fourteen patients have been described with well documented ARDS and profound (<500 PMN/mm^3) neutropenia (180,181). Eight of the 14 had typical ARDS histology on lung biopsy or autopsy, while six had pneumonia; in all fourteen, few or no PMNs were present in the lung. Thus, it is clear that ARDS can occur without PMNs. It is probable that ARDS occurred in these neutropenic patients due to direct toxic effects of LPS and TNF, as 13 of the 14 were thought to be septic prior to developing ARDS. Whatever the mechanism, ARDS in neutropenic patients demonstrates that multiple pathways can injure the lung and eventuate in ARDS.

Therapy of ARDS

Although understanding of the basic mechanisms producing ARDS has increased since the syndrome was first described in 1967, advances in ARDS therapy have not been marked. There are two reasons why current ARDS treatment frequently fails. First, therapy is largely supportive and is not directed at the underlying processes producing lung injury. Second, treatment is started too late; by the time a patient meets the diagnostic criteria for ARDS, cellular injury and severe disruption of normal lung function has already occurred. In the future, earlier identification of patients with ARDS risk factors may prevent ARDS by allowing earlier institution of anti-inflammatory therapy directed against the PMN. This section will review the current principles of ARDS management (Table 12).

TABLE 12

PRINCIPLES OF ARDS MANAGEMENT

- Maintain adequate oxygenation (PaO_2 > 55mmHg with an $FIO_2 \leq 50\%$)
- Avoid volume overload
- Diagnose and Treat Infection

Oxygenation and Positive End Expiratory Pressure (PEEP)

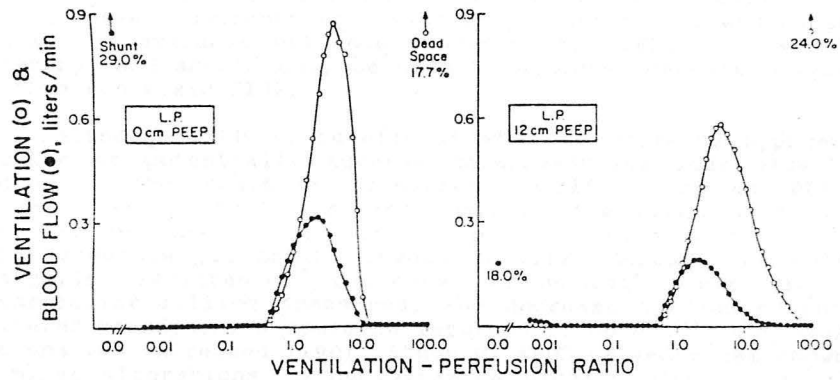
The initial priority in treating ARDS patients is usually correcting the severe hypoxemia. Although an adequate PaO_2 can sometimes be achieved with a tight fitting face mask delivering 100% FIO_2, patients usually fatigue, due to their increased work of breathing,and require endotracheal intubation and mechanical ventilation. Although an adequate PaO_2 can sometimes be acheived using standard modes of mechanical ventilation and 100% FIO_2, 100% oxygen should not be administered for longer than 24 hours. Exposure of normal humans to 100% O_2 for more than 24 hours causes a progressive decrease in PaO_2, decreased lung compliance, and increased intrapulmonary shunt blood flow (182). Prolonged periods of hyperoxia damage pulmonary epithelial and endothelial cells in vitro (182), and oxygen toxicity is a known cause of ARDS. Thus, if a patient cannot be oxygenated by standard mechanical ventilation with an $FIO_2 \leq 50\%$, positive end expiratory pressure (PEEP) should be started.

The use of PEEP for ARDS was first described in the same paper which initially reported ARDS (1). 3/5 patients treated with 5-10 cm H_2O PEEP survived, compared with 2/7 survivors treated with standard mechanical ventilation, and the authors

thought that PEEP might be beneficial; however, they made the prescient observation that "positive end expiratory pressure merely buys time: unless the underlying process can be successfully treated or reversed, the prognosis is grave." PEEP has been in wide use since 1967, and no prospective controlled trials have ever been performed to evaluate its efficacy. PEEP improves arterial oxygenation by preventing expiratory collapse of alveoli, thus increasing the functional residual capacity. Ventilation to previously airless alveoli is restored, resulting in a decrease in the amount of intrapulmonary shunt and an increase in the PaO_2. The effect of PEEP in reducing intrapulmonary shunt is shown graphically on Figure 14, which demonstrates a decrease in shunt flow from 29% to 18% with 12 cm PEEP.

FIGURE 14.

EFFECT OF PEEP ON INTRAPULMONARY SHUNT



Clinics Chest Med. 3:64, 1982.

In clinical use, PEEP should be increased by 5 cmH_2O increments until a PaO_2>55 mmHg can be obtained with an $FIO_2 \leq 50\%$. Once started, PEEP should never be abruptly discontinued, as a severe fall in PaO_2 may occur (184). Contraindications to PEEP include chronic obstructive lung disease, unilateral pulmonary disease, preextant hypovolemia, pneumothorax, or increased intracranial pressure (185).

There is no evidence that PEEP affects the underlying lung injury. In an animal ARDS model, no decrease in lung water content of PEEP treated animals was noted (186). A retrospective analysis of PEEP effect on survival has been performed. Seventy-eight patients were analyzed; 47 received PEEP, and mortality in

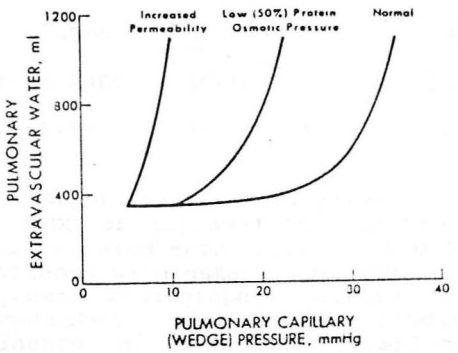
the PEEP group was 69%, similar to the 74% mortality of patients not receiving PEEP (187). The main effect of PEEP was to increase the mean time to death from 4.2 to 9.2 days. Although the study had flaws, and rigorous ARDS criteria were not used, it is interesting that patients not treated with PEEP were more ill (more were hypotensive and/or acidotic) than patients receiving PEEP and yet the mortality was similar.

The early use of PEEP (prophylactic PEEP) has been recommended by some to prevent the development of ARDS in at risk patients. One study of 79 intubated surgical patients reported a significant decrease in the incidence of ARDS when at risk (septic and/or severely injured) patients received 5 cm H_2O prophylactic PEEP. ARDS developed in 20% of the prophylactic PEEP patients compared to 53% of control patients, but the criteria used to diagnose ARDS were inadequate (188). A more recent investigation of the effect of 8cmH_2O prophylactic PEEP has been reported by Pepe (189), using correct diagnostic criteria for ARDS. A variety of medical and surgical patients at risk for ARDS were included. No difference in ARDS incidence, ARDS mortality, or time spent on mechanical ventilation was noted between patients receiving prophylactic PEEP and those not. Thus, the avilable evidence suggests that PEEP is a supportive therapy, and should only be used to achieve adequate oxygenation with a non-toxic FIO2.

Although PEEP is beneficial when it corrects hypoxemia, a number of potentially adverse cardiovascular side effects may occur. The positive pressures developed during PEEP are transmitted to the pulmonary vessels, the great veins in the thorax, and the pericardiac fossae. Animal studies have shown that moderate (12 cmH_2O) levels of PEEP increase the pulmonary vascular resistance, decrease transmural right and left ventricular filling pressures, and decrease cardiac output. The altered hemodynamics could be returned to normal if intravascular volume was increased (190). Study of ARDS patients has shown that similar alterations in hemodynamics usually occur only at PEEP levels of $\geq$ 15 cmH_2O, probably because the noncompliant lungs of ARDS transmit less of the positive pressure to the pleural space. Additionally, in humans PEEP induced increased pulmonary vascular resistance is associated with a shift of the interventricular septum into the left ventricular cavity, which impairs left ventricular filling (191). Because PEEP often decreases cardiac output, a fall in systemic oxygen transport, which is the product of arterial oxygen content and cardiac output, may occur if PEEP causes a greater fall in cardiac output than increase in arterial oxygen content (192) Patients receiving PEEP should be observed for a fall in systemic oxygen transport, by either serial cardiac output determinations or serial measurements of the mixed venous oxygen saturation, to detect adverse effects of PEEP on oxygen transport. PEEP induced decrements in blood pressure or cardiac output usually respond to intravascular volume challenges.

Other important goals of ARDS therapy are to avoid volume overload and diagnose and treat infections. The lungs of patients with increased permeability edema are especially sensitive to increased hydrostatic pressure. As shown on Figure 15, even normal pulmonary capillary wedge pressures (PCWP) tend to increase the amount of lung water present. For this reason, many authorities recommend keeping the PCWP as low as tolerated.

FIGURE 15



Textbook of Respiratory Medicine.
Murray and Nadel, Ed. pg.1295, 1988

Infection is a major complication of ARDS and contributes substantially to ARDS mortality (vide infra). Thus, vigorous preventive measures should be employed, and clinicians should have a high index of suspicion for infection when patients deteriorate.

Corticosteriods as Therapy for ARDS

The use of corticosteriods as therapy, especially as preventive therapy, for ARDS has been attractive due to the <u>in vitro</u> and <u>in vivo</u> anti-inflammatory effects of steriods (193). In a human study of septic patients in respiratory failure, Sibbald demonstrated a decreased appearance of radiolabeled albumin in BAL fluid when patients received corticosteriods (methylprednisolone 30mg/kg Q 6 hr x 4) (193). Two large, randomized clinical trials have been performed to investigate the use of steriods in septic shock. Both studies entered patients within 2 hrs of shock onset, analyzed only patients with positive blood cultures, and compared the results of early methyprednisolone treatment (30mg/kg Q 6 hr x 4) to placebo

(195,196). The results of the larger of the two studies (304 patients) are summarized on Table 13.

TABLE 13

ARDS in Corticosteroid and Placebo Treated Septic Shock Patients

	Treatment Group			
	Steroid		Placebo	
	N	%	N	%
Incidence of ARDS	50/152	32	38/152	25
Recovery from ARDS	15/50	31	23/38	61
14 Day Mortality	26/50	52	8/38	21

Neither study found that methylprednisolone prevented the development of ARDS or improved the outcome of ARDS. Another investigator has compared methylprednisolone to a placebo for the treatment of patients with established ARDS (196). No difference in mortality, chest radiographic improvement, or gas exchange could be demonstrated. One of the studies cited found an increased incidence of infectious complications in steriod treated patients (198), and an increased infection rate has been reported in another study of septic shock patients receiving similar steroid doses (199). Since steriods are ineffective in preventing sepsis associated ARDS and in treating established ARDS, and corticosteriod administration is associated with an increased risk of infection, corticosteriods should not be given routinely to ARDS patients. One important exception may be patients with multiple long bone/pelvic fractures, in whom the early administration of methylprednisolone reduces the incidence of the fat embolism syndrome (200).

Outcome of ARDS

The prognosis for patients with ARDS is poor, with most large series over the past decade reporting a mortality rate of from 65-78%. For comparative purposes, the mortality rate in the original 1967 series was 58%. Despite the high mortality, patients surviving ARDS usually have only minimal impairment of pulmonary function. Two studies of survivors have been performed. The subjects in both studies were minimally symptomatic, 80% had normal vital capacity, and 50% had a normal diffusion capacity for carbon monoxide (DLCO). Resting PaO_2 was normal in 88%, but a decreased PaO_2 was noted with exercise in 70% (201,202). In a follow up report on one group of ARDS survivors, three patients were noted to have acquired evidence of reactive airways disease (203). Survival with adequate lung function, despite the presence of large amounts of fibrosis on lung biopsy, has been noted (15). Thus, despite prolonged

periods of mechanical ventilation, patients can recover with minimal impairment.

Prognostic markers in ARDS have not been extensively studied. The negative prognostic importance of a persistently elevated pulmonary vascular resistance has been discussed previously. Lamy (15) investigated the relationships between lung histology (biopsy or autopsy specimens), the PaO_2 response to PEEP, and mortality in 45 consecutive patients. A scoring system was devised to quantitate the amount of acute inflammation and fibrosis present, and patients were divided into three groups, based on the response of their PaO_2 to 10 cmH_2O PEEP. The findings are summarized on Table 14.

Table 14

	Patient Group		
	I	II	III
Response to PEEP* (mmHg)	2+4	15+8 +	68+59
Acute Inflammation Score	22+5	13+7	18+6
Fibrosis Score	4±2	9±4	2±2
Mortality (%)	82	77	50

* Increase in PaO_2 with 10 cmH_2O PEEP

\+ Delayed increase, requiring 30 minutes

Group I patients had the largest amount of inflammation, a minimal response to PEEP, and the highest mortality. Group II patients were characterized by a delayed increase in PaO_2, and had the most fibrosis and high mortality. Group III patients had a moderate amount of inflammation, a large PaO_2 response to PEEP, minimal fibrosis, and the best survival. Springer (187) also reported that large increases in PaO_2 with PEEP were associated with an improved survival. A prospective study of prognostic factors in 88 ARDS patients has been performed. The influence on mortality of a large number of factors present at the time of ARDS diagnosis was investigated by a proportional hazards model; response of PaO2 to PEEP was not included. Three factors - < 10% PMN band forms on the CBC, blood pH <7.40 (on mechanical ventilation), and serum HCO3 concentrations of <20 mg% - were associated with a 2-2.7 excess risk of mortality (204).

It is becoming increasingly evident that death in ARDS rarely occurs from respiratory failure per se. PEEP therapy and improved intensive care have prevented ARDS patients from early

death due to acute respiratory failure, but patients subsequently develop complications, particularly infections and multiple organ system failure, and die at a later date. Bell (205) reported on 141 consecutive ARDS patients, 104 of whom died (47 had autopsies). Only 2 of the 104 patients were thought to have died from hypoxemia. At ARDS onset, the degree of pulmonary impairment and the presence of nonpulmonary organ system failure was similar in survivors and nonsurvivors. Non-survivors developed multiorgan system failure significantly more often than survivors, and multiorgan failure was related to infection, as 93% of patients with an antemortem infection diagnosis developed multiorgan failure, versus 47% of patients without infection. Evidence of infection was present in 90% of the autopsied nonsurvivors, and 40% of autopsies revealed a clinically unsuspected infection, usually in the lung, pleural space, or abdomen, even though virtually all patients had been treated with antibiotics. The difficulty of diagnosing pneumonia antemortem in ARDS has been previously demonstrated (206). Similar results have been reported from Montgomery in a series of 47 ARDS patients, 32 of whom died (207). In only 16% was death judged to be directly due to respiratory failure. Death frequently occurred due to sepsis (34%), followed by cardiac, central nervous system, and hematologic organ system failure. Sepsis, as either a direct or contributing cause of death, occurred in 70%, and a pulmonary source of sepsis was present in 75%. It is obvious from these two studies that the major obstacle to survival in ARDS today is the development of multiorgan system failure, precipitated in most instances by infection. Thus, it is likely that improvement in ARDS outcome will depend heavily on preventing infections in these critically ill patients.

REFERENCES

1. Ashbaugh, D.G., et al. Acute respiratory distress in adults. Lancet 2:319, 1967.

2. Hudson, L.D. Causes of the adult respiratory distress syndrome. Clinics Chest Med. 3:195, 1982.

3. Connors, A.F. Jr., et al. Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. NEJM. 308:263, 1983.

4. Fein, A.M., et al. Is pulmonary artery catheterization necessary for the diagnosis of pulmonary edema. Amer. Rev. Resp. Dis. 129:1006, 1984.

5. Fowler, A.A., et al. Adult respiratory distress syndrome: risk with common predispositions. Annals of Int. Med. 98:593, 1983.

6. Pepe, P.E., et al. Clinical predictors of the adult respiratory distress syndrome. Amer. J. Surgery. 144:124, 1982.

7. Diffuse alveolar damage. in Surgical Pathology of Non-Neoplastic Lung Disease. Katzenstein, A.A., F.B. Askin, Editors. W.B. Saunders Co., 1982.

8. Bachofen, M. and E.R. Weibel. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clinics Chest Med. 3:35, 1982.

9. Hill, J.D., et al. Pulmonary pathology in acute respiratory insufficiency: lung biopsy as a diagnostic tool. J. of Thoracic and Cardiovascular Surgery. 71:64,1976.

10. Bachofen, M. and E.R. Weibel. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. Amer. Rev. Resp. Dis. 116:589, 1977.

11. Nash, G., et al. Pulmonary interstitial edema and hyaline membranes in adult burn patients. Human Path. 5:149, 1974.

12. Tomashefski, J.E.Jr. et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. Amer. J. Path. 112:112, 1983.

13. Zapol, W.M. et al. Pulmonary fibrosis in severe acute respiratory failure. Amer. Rev. Resp. Dis. 119:547, 1979.

14. Collins, J.E. et al. Variability in lung collagen amounts after prolonged support of acute respiratory failure. Chest. 85:641, 1984.

15. Lamy, M., et al. Pathologic Features and Mechanisms of Hypoxemia in Adult Respiratory Distress Syndrome. Amer. Rev. Resp. Dis. 114:267, 1976.

16. Seppa, H., et al. Platelet-derived growth factor is chemotactic for fibroblasts. J. Cell Bio. 92:584, 1982.

17. Deuel, T.F. and J.S. Huang. Platelet-derived growth factor: structure, function and roles in normal and transformed cells. J. Clin. Invest. 74:669, 1984.

18. Bitterman, P.B., et al. Mechanisms of pulmonary fibrosis. Spontaneous release of the alveolar macrophage-derived growth factor in the interstial lung disorders. J. Clin. Invest. 72:1801, 1983.

19. Bitterman, P.B., et al. Human alveolar macrophage growth factor for fibroblasts. J. Clin. Invest. 70:806, 1982.

20. Leibovich, S.J. and R. Ross. A macrophage-dependent factor that stimulates the proliferation of fibroblasts in vitro. Amer. J. Path. 84:501, 1976.

21. Staub, N.C. The pathogenesis of pulmonary edema. Amer. Rev. Resp. Dis. 109:358, 1974.

22. Crandall, E.D, et al. Recent developments in pulmonary edema. Annals Int. Med. 99:808, 1983.

23. Szidon, J.P., et al. The alveolar-capillary membrane and pulmonary edema. NEJM. 286:1200, 1972.

24. Schneeberger, E.E. Structural basis for some permeability proterties of the air-blood barrier. Fed. Proc. 37:2471, 1978.

25. Matthay, M.A. Resolution of pulmonary edema. Clinics Chest Med. 6:521, 1985.

26. Montaner, J.S.G., et al. Alveolar epithelial damage. A critical difference between high pressure and oleic acid-induced low pressure pulmonary edema. J. Clin. Invest. 77:1786, 1986.

27. Barrios, R., et al. Intercellular junctions in shock lung - a freeze-fracture study. Lab. Invest. 36:628, 1977.

28. Anderson, R.R., et al. Documentation of pulmonary capillary permeability in the adult respiratory distress syndrome accompanying human sepsis. Amer. Rev. Resp. Dis. 119:869, 1979.

29. Sprung, C.L., et al. The spectrum of pulmonary edema: Differentiation of cardiogenic, intermediate and noncardiogenic forms of pulmonary edema. Amer. Rev. Resp. Dis. 124:718, 1981.

30. Fein, A., et al. The value of edema fluid protein measurement in patients with pulmonary edema. Amer. J. Med. 67:32, 1979.

31. Holter, J.F., et al . Protein permeability in the adult respiratory distress syndrome. Loss of size selectivity of the alveolar epithelium. J. Clin. Invest.. 78:1513, 1986.

32. Pontoppidan, H., et al. Acute respiratory failure in the adult. (Three part article) NEJM. 287:690, 743, 799, 1972.

33. Hallman, Mikko, et al. Evidence of lung surfactant abnormality in respiratory failure. J. Clin. Invest. 70:673, 1982.

34. Petty, T.L., et al. Abnormalities in lung elastic proterties and surfactant function in adult respiratory distress syndrome. Chest. 75:571, 1979.

35. Albert, R. K., et al. Increased surface tension favors pulmonary edema formation in anesthetized dogs' lungs. J. Clin. Invest. 63:1015, 1979.

36. Dantzker, D.R., et al. Ventilation-perfusion distribution in ARDS. Amer. Rev. Resp. Dis. 120:1039, 1979.

37. West, J.B. Ventilation-Perfusion Relationships. Amer. Rev. Resp. Dis. 116:919, 1977.

38. Zapol, W. M. and M.R. Snider. Pulmonary hypertension in severe acute respiratory failure. NEJM. 296:476, 1977.

39. Zapol, W.M., et al. Pulmonary circulation during adult respiratory distress syndrome. in Acute Respiratory Failure. W.M. Zapol, K.J. Falke, Editors. Marcel Dekker, 1985.

40. Greene, R., et al. Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. Amer. Rev. Resp. Dis. 124:593, 1981.

41. Snow, R.L., et al. Pulmonary vascular remodeling in adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 126:887, 1982.

42. Robin, E.D., et al. Pulmonary Edema (Two Parts). NEJM. 288: 239, 292, 1973.

43. Brigham. K., et al. Correlation of oxygenation with vascular permeability-surface area but not with lung water in humans with acute respiratory failure and pulmonary edema. J. Clin. Invest. 72:339, 1983.

44. Rinaldo, J.E. and R.M. Rogers. Acute respiratory distress syndrome. NEJM. 315:578, 1986.

45. Heffner, J.E., et al. Acetyl glyceryl ether phosphorycholine-stimulated human platelets cause pulmonary hypertension and edema in isolated rabbit lungs. J. Clin. Invest. 71:351, 1983.

46. Chang, S.W., et al. Platelet-activating factor mediates hemo-dynamic changes and lung injury in endotoxin-treated rats. J. Clin. Invest. 79:1498, 1987.

47. Movat, H.Z., et al. Acute inflammation in gram negative infection: endotoxin, interleukin 1, tumor necrosis factor, and neutrophils. Fed. Proc. 46:97, 1987.

48. Martin, T.R., et al. Relative contribution of leukotriene B_4 to neutrophil chemotactic activity produced by the resident human alveolar macrophage. J. Clin. Invest. 80:1114, 1987.

49. Hoover, R.L., et al. Leukotriene B_4 action on endothelium mediates augmented neutrophil/endothelial adhesion. Proc. Nat. Acad. Sci. 81:2191, 1984.

50. Lewis, R.A., et al. The biologically active leukotrienes, biosynthesis, metabolism, receptors, functions and pharmacology. J. Clin. Invest.73:889, 1984.

51. Levin, J., et al. Detection of endotoxin in the blood of patients with sepsis due to gram-negative bacteria. NEJM. 24:1313, 1973.

52. Smedly, L.A., et al. Neutrophil-mediated injury to endothelial cells. J. Clin. Invest. 77:1233, 1986.

53. Mathison, J.C., et al. Participation of tumor necrosis factor in the mediation of gram negative bacterial lipopolysaccharide-induced injury in rabbits. J. Clin. Invest. 81:1925, 1988.

54. Forehand, J.R., et al. Lipopolysaccharide priming of human neutrophils for an enhanced respiratory burst. J. Clin. Invest. 83:74, 1989.

55. Pohlman, T.H., et al. An endothelial cell surface factor(s) induced in vitro by lipopolysaccharide, interleukin 1, and tumor necrosis factor-alpha increases neutrophil adherence by a CDw18-dependent mechanism. J. Immun. 136:4548, 1986.

56. Strieter, R.M., et al. Endothelial cell gene expression of a neutrophil chemotactic factor by TNF-alpha, LPS, and IL-1 beta. Science. 243:1467, 1989.

57. Colucci, M., et al. Cultured human endothelial cells generate tissue factor in response to endotoxin. J. Clin. Invest. 71:1893, 1983.

58. Meyrick, B.O., et al. Direct effects of E coli endotoxin on structure and permeability of pulmonary endothelial monolayers and the endothelial layer of intimal explants. Amer. J. Path. 122:140, 1986.

59. Harlan, J.M., et al. Lipopolysaccharide-mediated bovine endothelial cell injury in vitro. Lab. Invest. 48:269, 1983.

60. Fearon, D.T., et al. Activation of the properdin pathway of complement in patients with gram-negative bacteremia. NEJM. 292:937, 1975.

61. Beutler, B. and A. Cerami. Cachectin: more than a tumor necrosis factor. NEJM. 316:379, 1987.

62. Tracey, K.J., et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteremia. Nature. 330:662, 1987.

63. Hesse, D.G., et al. Cytokine appearance in human endotoxemia and primate bacteremia. Surgery, Gynecology and Obstetrics. 166:147, 1988.

64. Tracey, K.J., et al. Shock and tissue injury induced by recombinant human cachectin. Science. 234:470, 1986.

65. Tracey, K.J., et al. Cachectin/tumor necrosis factor induces lethal shock and stress hormone responses in the dog. Surgery, Gynecology, and Obstetrics. 164:415, 1987.

66. Larrick, J.W., et al. Recombinant tumor necrosis factor causes activation of human granulocytes. Blood. 69:640, 1987.

67. Klebanoff, S. J., et al. Stimulation of neutrophils by tumor necrosis factor. J. Immun. 136:4220, 1986.

68. Gamble, J.R., et al. Stimulation of the adherence of neutrophils to umbilical vein endothelium by recombinant tumor necrosis factor. Proc. Nat. Acad. Sci. 82:8667, 1985.

69. Nawroth, P.P. and D.M. Stern. Modulation of endothelial cell hemostatic proterties by tumor necrosis factor. J. Exp. Med. 163:740, 1986.

70. Nawroth, P.P., et al. Tumor necrosis factor/cachectin interacts with endothelial cell receptors to induce release of interleukin 1. J. Exp. Med. 163:1363, 1986.

71. Moser, R., et al.Interleukin 1 and tumor necrosis factor stimulate human vascular endothelial cells to promote transendothelial neutrophil passage.J. Clin. Invest. 83:444, 1989.

72. Stolpen, A.H., et al. Recombinant tumor necrosis factor and immune interferon act singly and in combination to reorganize human vascular endothelial cell monolayers. Amer. J. Path. 123:16, 1986.

73. Stephens, K.E., et al. Tumor necrosis factor causes increased pulmonary permeability and edema. Amer. Rev. Resp. Dis. 137:1364.

74. Michie, H.R., et al. Detection of circulating tumor necrosis factor after endotoxin administration. NEJM. 318:1481, 1988.

75. Waage, A., et al. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet. 1:355, 1987.

76. Tracey, K.J., et al. Cachetin/TNF-alpha in septic shock and septic adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 138:1377, 1988.

77. Ziegler, E.J. Tumor necrosis factor in humans. NEJM. 318:1533, 1988.

78. Till, G.O., et al. Oxygen radical dependent lung damage following thermal injury of rat skin. J. of Trauma. 23:269, 1983.

79. Heideman, M., et al. Complement activation and hematologic, hemodynamic and respiratory reactions early after soft-tissue injury. J. of Trauma. 18:696, 1978.

80. Goldstein, I.M. Complement: biologically active products in Inflammation. Gallin, J.I., I.M. Goldstein and R. Snyderman, Editors. Raven Press, 1988.

81. Hammerschmidt, D.E., et al. Association of complement activation and elevated plasma-C5a with adult respiratory distress syndrome. Lancet. I:947, 1980.

82. Solomkin, J.S., et al. Complement activation and clearance in acute illness and injury: evidence for C5a as a cell-directed mediator of the adult respiratory distress syndrome in man. Surgery. 97:668, 1985.

83. Duchateau, J., et al. Complement activation in patients at risk of developing the adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 130:1058, 1984.

84. Weinberg, P.F., et al. Biologically active products of complement and acute lung injury with the sepsis syndrome. Amer. Rev. Resp. Dis. 130:791, 1984.

85. Langlois, P.F. and M.S. Gawryl. Accentuated formation fo the terminal C5b-9 complement complex in patient plasma precedes development of the adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 138:368, 1988.

86. Desai, U., et al. Acute inflammatory pulmonary reactions induced by chemotactic factors. Amer. J. Path. 96:71, 1979.

87. Webster, R.O.,et al. Absence of inflammatory lung injury in rabbits challenged intravascularly with complement-derived chemotactic factors. Amer. Rev. Resp. Dis. 125:335, 1982.

88. Shaw, J.O. and P.M. Henson. Pulmonary intravascular sequestration of activated neutrophils. Amer. J. Path. 108:17, 1982.

89. Craddock, P.R., et al. Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. J. Clin. Invest. 59:879, 1977.

90. Craddock, P.R., et al. Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. NEJM. 296:669, 1977.

91. Worthen, G.S., et al. Synergistic effect of trace amounts of lipopolysaccharide and neutrophil stimuli on vascular permeability and neutrophil sequestration in the lung. Amer. Rev. Resp. Dis. 136:19, 1987.

92. Larsen, G.L., et al. Additive effect of intravascular complement activation and brief episodes of hypoxia in producing increased permeability in the rabbit lung. J. Clin. Invest. 75:902, 1985.

93. Nielsen, S.O. Pulmonary alveolar hypoxia: release of prostaglandins and other humoral mediators. Science. 185:1181, 1974.

94. Cohen, A.B. and M. Rossi. Neutrophils in normal lungs. Amer. Rev. Resp. Dis. 127:S3, 1983.

95. Worthen, G.S., et al. Interaction of leukocytes with the pulmonary endothelium in pulmonary endothelium. in The Pulmonary Endothelium Health and Disease. U.S. Ryan, Editor. Macel Dekker, 1987.

96. Schlag, G., H.R. Redl. Morphology of the human lung after traumatic injury. in Acute Respiratory Failure. W.M. Zapol, Editor. Marcel Dekker, 1985.

97. Weiland, J.E., et al. Lung neutrophils in the adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 133:218, 1986.

98. Parson, P.E., et al.Chemotactic activity in bronchoalveolar lavage fluid from patients with adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 132:490, 1985.

99. Christner, P., et al. Collagenase in the lower respiratory tract of patients with adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 131:690, 1985.

100. Fowler, A.A., et al. The adult respiratory distress syndrome. Cell populations and soluble mediators in the air spaces of patients at high risk. Amer. Rev. Resp. Dis. 136:1225, 1987.

101. Lee, C.T., et al. Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory-distress syndrome. NEJM. 304:192, 1981.

102. Rinaldo, J.E. and H. Borovetz. Deterioration of oxygenation and abnormal lung microbvascular permeability during resolution of leukopenia in patients with diffuse lung injury. Amer. Rev. Resp. Dis. 131:579, 1985.

103. Staub, N.C., et al. Preparation of chronic lung lymph fistulas in sheep. J. of Surgical Res. 19:315, 1975.

104. Brigham, K.L., et al.Increased sheep lung vascular permeability caused by pseudomonas bacteremia. J. Clin. Invest. 54:792, 1974.

105. Brigham, K.L., et al. Increased sheep lung vascular permeability caused by Escherichia coli endotoxin. Circ. Res. 45:292, 1979.

106. Snapper, J.R., et al.Endotoxemia-induced leukopenia in sheep. Amer. Rev. Resp. Dis. 127:306, 1983.

107. Meyrick, B. and K.L. Brigham. Acute effects of Escherichia coli endotoxin on the pulmonary microcirculation of anesthetized sheep. Lab. Invest. 48:458, 1983.

108. Meyrick, B.O., K.L. Brigham. The effect of a single infusion of zymosan-activated plasma on the pulmoanry microcirculation of sheep. Amer. J. Path. 114:32, 1984.

109. Hinson, J.M., et al. Effect of granulocyte depletion on altered lung mechanics after endotoxemia in sheep. J. App. Phys. 55(1):92, 1983.

110. Helfin Jr., A.C. and K.L. Brigham. Prevention by Granulocyte depletion of increased vascular permeability of sheep lung following endothoxemia. J. Clin. Invest. 68:1253, 1981.

111. Brigham, K.L., et al. Methylprednisolone prevention of increased lung vascular permeability following endotoxemia in sheep. J. Clin. Invest. 67:1103, 1981.

112. Winn, R., et al. Thromboxane A_2 mediates lung vasoconstriction but not permeability after endotoxin. J. Clin. Invest. 72:911, 1983.

113. Ogletree, M.L. and K.L. Brigham. Arachidonate raises vascular resistance but not permeability in lungs of awake sheep. J. App. Phys. 48(4):581, 1980.

114. Hales, C.A., et al. Role of thromboxane and prostacyclin in pulmonary vasomotor changes after endotoxin in dogs. J. of Clin. Invest. 68:497, 1981.

115. Synderman, R. and R.J. Whing. Phagocytic cells: stimulus response coupling. in Inflammation. J.I. Gallin, R. Snyderman, Editors. Raven Press, 1988.

116. Dahinden, C.A., et al. Role of cell surface contact in the kinetics of superoxide production by granulocytes. J. Clin. Invest. 72:113, 1983.

117. Nathan, C.F. Neutrophil activation on biological surfaces. J. Clin. Invest. 80:1550, 1987.

118. Dahinden, C.and J. Fehr. Granulocyte activation by endotoxin. J. Immun. 130:863, 1983.

119. Crowley, C.A., et al. An inherited abnormality in neutrophil adhesion; its genetic transmission and its association with a missing protein. NEJM. 302:1163, 1980.

120. Anderson, D.C. and T.A. Springer. Leukocyte adhesion deficiency: an inherited defect in the Mac-1, LFA-1, and p150,95 glycoproteins. Annual Review of Medicine. 38:174, 1987.

121. Arnaout, M.A., et al. Deficiency of a leukocyte surface glycoprotein (LFA-1) in two patients with Mol deficiency. J. Clin. Invest. 74:1291, 1984.

122. Fearon, D.T. and L.A. Collins. Increased expression of C3b receptors on polymorphonuclear leukocytes induced by chemotatic factors and by purification procedures. J. of Immun. 130:370, 1983.

123. Bainton, D.F., et al. Leukocyte adhesion receptors are stored in peroxidase-negative granules of human neutrophils. J. Exp. Med. 166:1641. 1987.

124. Zimmerman, G.A. and T.M. McIntyre. Neutrophil adherence to human endothelium in vitro occurs by CDw18 (Mo1, MAC-1/LFA-1/GP 150,95). J. Clin. Invest. 81:531, 1988.

125. Wallis, W.J., et al. Monoclonal antibody-defined functional epitopes on the adhesion-promoting glycoprotein complex (CDw18) of human neutrophils. Blood. 67:1007, 1986.

126. Vedder, N.B. and J.M. Harlan. Increased surface expression of CD11b/CD18 (Mac-1) is not required for stimulated neutrophil adherence to cultured endothelium. J. Clin. Invest. 81:676, 1988.

127. Arnaout, M.A., et al. Increased expression of an adhesion-promoting surface glycoprotein in the granulocytopenia of hemodialysis. NEJM. 312:457, 1985.

128. Zimmerman, G.A., et al. Functional and metabolic activity of granulocytes from patients with adult respiratory distress syndrome. Amer. Rev. Resp. Dis. 127:290, 1983.

129. Thommasen, H.V., et al.Transient leukopenia associated with adult respiratory distress syndrome. Lancet. 1:809, 1984.

130. Ismail, G., et al.Prevention of pulmonary injury in isolated perfused rat lungs by activated human neutrophils preincubated with anti-Mo1 monoclonal antibody. Blood. 69(4):1167, 1987.

131. Simon, R.H., et al. Neutrophil-induced injury of rat pulmonary alveolar epithelial cells. J. Clin. Invest. 78:1375, 1986.

132. Pober, J.S., et al. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J. Immun. 137:1893, 1986.

133. Dustin, M.L.,. Induction by IL 1 and interferon-gamma:tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). J. Immun. 137:245, 1986.

134. Smith, C.W., et al. Recognition of an endothelial determinant for CD18-dependent human neutrophil adherence and transendothelial migration. J. Clin. Invest. 82:1746, 1988.

135. Bevilacqua, M.P., et al. Identification of an inducible endothelial-leukocyte adhesion molecule. Proc. Nat. Acad. Sci. 84:9238, 1987.

136. Bevilacqua, M.P., et al. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science. 243:1160, 1989.

137. Cotran, R.S., et al. Induction and detection of a human endothelial activation antigen in vivo. J. Exp. Med. 164:661, 1986.

138. Weiss, S.J., et al. Role of hydrogen peroxide in neutrophil-mediated destruction of cultured endothelial cells. J. Clin. Invest. 68:714, 1981.

139. Harlan, J.M., et al.Glutathione redox cycle protects cultured endothelial cells against lysis by extracellularly generated hydrogen peroxide. J. Clin. Invest. 73:706, 1984.

140. Nathan, C.F. and S.J. Klebanoff. Augmentation of spontaneous macrophage-mediated cytolysis by eosinophil peroxidase. J. Exp. Med. 155:1291, 1982.

141. Weiss, S.J., et al. Chlorination of Taurine by Human Neutrophils. J. Clin. Invest.. 70:598, 1982.

142. Weiss, S.J. Tissue distruction by neutrophils. NEJM 320:365, 1989.

143. Albrich, A.M., et al. Effects of the putative neutrophil-generated toxin, hypoclorous acid, on membrane permeability and transport systems of esherichia coli. J. Clin. Invest. 78:177, 1986.

144. Suttorp, N. and L.M. Simon. Lung Cell Oxidant Injury: Enhancement of polymorphonuclear leukocyte-mediated cytotoxicity in lung cells exposed to sustained in vitro hyperoxia. J. Clin. Invest. 70:342, 1982.

145. Sacks, T., et al. Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes. J. Clin. Invest. 78:1161, 1978.

146. Shasby, D.M., et al. Granulocytes and phorbol myristate acetate increase permeability to albumin of cultured endothelial monolayers and isolated perfused lungs. Amer. Rev. Resp. Dis. 127:72, 1983.

147. Shasby, D.M., et al. Granulocytes mediate acute edematous lung injury in rabbits and in isolated rabbit lungs perfused with phorbol myristate acetate: role of oxygen radicals. Amer. Rev. Resp. Dis. 125:443, 1982.

148. Dakin, H.D. The behavior of hypoclorites on intravenous injection and their action on blood serum. Br. Med. J. 1:852, 1916.

149. Johnson, K.J.,et al. In vivo damage of rat lungs by oxygen metabolites. J. Clin. Invest. 67:983, 1981.

150. Till, G.O., et al.Intravascular activation of complement and acute lung injury. J. Clin. Invest. 69:1126, 1982.

151. Ward, P.A., et al. Systemic complement activation, lung injury, and products of lipid peroxidation. J. Clin. Invest. 76:517, 1985.

152. Johnson, K.J., and P.A. Ward. Role of oxygen metabolites in immune complex injury of lung. J. Immun. 126:2365, 1981.

153. Baldwin, S.R., et al. Oxidant activity in expired breath of patients with adult respiratory distress syndrome. Lancet I:11, 1986.

154. Weiss, S.J., et al. Oxidative autoactivation of latent collagenase by human neutrophils. Science 227:747, 1985.

155. Clark, R.A.,et al. Myeloperoxidase-catalyzed inactivation of alpha 1 protease inhibitor by human neutrophils. J. Bio. Chem. 256:3348, 1981.

156. Ossanna, P.J., et al . Oxidative regulation of neutrophil elastase-alpha 1 proteinase inhibitor interactions. J. Clin. Invest. 77:1939, 1986.

157. Wasil, M., et al. The antioxidant action of human extracellular fluids. Biochem. Journal. 243:219, 1987.

158. McGuire, W.W., et al. Studies on the pathogenesis of the adult respiratory distress syndrome.J. Clin. Invest. 69:543, 1982.

159. Cochrane, C.G., et al. Pathogenesis of the adult respiratory distress syndrome. J. Clin. Invest. 71:754, 1983.

160. Wewers, M.D., et al. Alveolar fluid neutrophil elastase activity in the adult respiratory distress syndrome is complexed to alhpa-2-macroglobulin.J. Clin. Invest. 82:1260, 1988.

161. Fowler, A.A., et al. Characterization of antiproteinase activity in the adult respiratory distress syndrome. Chest 81:5, 1982.

162. Schmidt, William. Differential release of elastase and chymotrypsin from polynmorphonuclear leukocytes. Neutral Proteases of Human Polymorphonuclear Leukocytes. K.Havemann and A. Janoff, Editors. Urban and Schwarzenberg, 1978.

163. McDonald, J.A. and D.G. Kelley. Degradation of fibronectin by human leukocyte elastase. J. Biol. Chem. 255:8848, 1980.

164. Gadek, J.E., et al. Human neutrophil elastase functions as a type III collagen "collagenase". Biochem. Biophys. Res. Comm. 95:1815, 1980.

165. Mainardi, C.L., et al. Degradation of type IV (basement membrane) collagen by a proteinase isolated from human polymorphonuclear leukocyte granules.J. Bio. Chem. 255:5435, 1980.

166. Harlan, J.M., et al. Activated neutrophils disrupt endothelial monolayer integrity by an oxygen radical-independent mechanism. Lab. Invest. 52:141, 1985.

167. Harlan, J.M., et al. Neutrophil-mediated endothelial injury in vitro. J. Clin. Invest. 68:1394, 1981.

168. Movat, H.Z. and S. Wasi. Severe microvascular injury induced by lysosomal releasates of human polymorphonuclear leukocytes. Amer. J. Path. 121:404, 1985.

169. Janoff, Aaron. Mediators of tissue damage in leukocyte lysosomes. Lab. Invest. 22:228, 1970.

170. Janoff, A. and J.D. Zeligs. Vascular injury and lysis of basement membrane in vitro by neutral protease of human leukocytes. Science 161:702,1968.

171. Cochrane, C.G. and B.S. Aikin. Polymorphonuclear leukocytes in immunologic reactions. J. Exp. Med.124:733, 1966.

172. Morgan, L., et al. Elastin degradation in the adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 127:A93, 1983.

173. Idell, S. Neutrophil elastase releasing factors in bronchoalveolar lavage from patients with ARDS Amer. Rev. Resp. Dis. 132:1098, 1985.

174. Martin, T.R. et al. The effects of chronic bronchitis and chronic air-flow obstruction on lung cell populations recovered by bronchoalveolar lavage. Amer.Rev.Resp.Dis. 132:254, 1985.

175. Wright, S.D. and S. C Silverstein. Phagocytosing macrophages exclude proteins from the zones of contact with opsonized targets. Nature. 309:359, 1984.

176. Campbell, E.J., et al. Proteolysis by neutrophils. Relative importance of cell-substrate contact and exidative in activation of proteinase inhibitors in vitro. J. Clin. Invest. 70:845, 1982.

177. Campbell, E.J., and M.A. Campbell. Pericellular proteolysis by neutrophils in the presence of proteinase inhibitors: effects of substrate opsonization. J. Cell Bio. 106:667, 1988.

178. Weiss, S.J. and S. Regiani. Neutrophils degrade subendothelial matrices in the presence of alpha-1-proteinase inhibitor. J.Clin. Invest. 73:1297, 1984.

179. Weitz, J.I., et al. Elastase-mediated fibrinogenolysis by chemoattractant-stimulated neutrophils occurs in the presence of physiologic concentrations of antiproteinases. J. Exp. Med. 166:1836, 1987.

180. Ognibene, F.P., et al. Adult respiratory distress syndrome in patients with severe neutropenia. NEJM. 315:547, 1986.

181. Maunder, R.J.,et al. Occurrence of the adult respiratory distress syndrome in neutropenic patients. Amer.Rev.Resp.Dis 133:313, 1986.

182. Barber, R.E., et al. Oxygen Toxicity in Man. A prospective study in patients with irreversible brain damage. NEJM. 283:1478, 1970.

183. Martin, W.J., et al. Oxidant injury of lung parenchymal cells. J. Clin. Invest. 68:1277, 1981.

184. Weisman, I.M., et al. Positive end-expiratory pressure in adult respiratory failure. NEJM. 307:1381, 1982.

185. Gong, H. Positive-pressure ventilation in the adult respiratory distress syndrome. Clinics Chest Med. 3:69, 1982.

186. Hopewell, P.C. Failure of positive end-expiratory pressure to decrease lung water content in alloxan-induced pulmonary edema. Amer. Rev. Resp. Dis. 120:813, 1979.

187. Springer, R.R., and P.M. Stevens. The influence of PEEP on survical of patients in respiratory failure. Amer.J.Med. 66:196, 1979.

188. Weigelt, J.A., et al. Early positive end-expiratory pressure in the adult respiratory distress syndrome. Archives Surgery. 114:497, 1979.

189. Pepe, E.P., et al. Early application of positive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. NEJM. 311:281, 1984.

190. Qvist, J., et al. Hemodynamic responses to mechanical ventilation with PEEP. Anesthesiology. 42:45, 1975.

191. Jardin, F., et al. Influence of positive end-expiratory pressure on left ventricular performance. NEJM. 304:387, 1981.

192. Lutch, J.S., and J.F. Murray. Continuous positive-pressure ventilation: effects on systemic oxygen transport and tissue oxygenation. Annals Int. Med. 76:193, 1972.

193. Hammerschmidt, D.E., et al. Corticosteroids inhibit complement-induced granulocyte aggregation: a possible mechanism for their efficacy in shock states. J.Clin. Invest. 63:798, 1979.

194. Sibbald, W.J., et al. Alveolo-capillary permeability in human septic ARDS: effect of high dose corticosteroid therapy. Chest 79:133, 1981.

195. Bone, R.C., et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. NEJM 317:653, 1987.

196. Luce, J.M., et al. Ineffectiveness of high-dose methyl-prednisolone inpreventing parenchymal lung injury and improving mortality in patients with septic shock. Amer. Rev. Resp. Dis. 138:62, 1988.

197. Bernard, G.R., et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. NEJM. 317:1565, 1987.

198. Bone, R.C., et al. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest. 92:1032, 1987.

199. Sprung, C.L., et al. The effects of high-dose cortico-steriods in patients with septic shock. NEJM. 311:1137, 1984.

200. Schonfeld, S.A., et al. Fat embolsim prophylaxis with corticosteroids. Annals Int. Med. 99:438, 1983.

201. Lakshminarayan, S., et al. Prognosis after recovery from adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 113:7, 1976.

202. Elliott, C.G., et al. Pulmonary function and exercise gas exchange in survivors of adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 123:492, 1981.

203. Simpson, D.L., et al. Long-term followup and bronchial reactivity testing in survivors of the adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 117:449, 1978.

204. Fowler, A.A., et al. Adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 132:472, 1985.

205. Bell, R.C., et al. Multiple organ system failure and infection in adult respiratory distress syndrome. Annals Int. Med. 99:293, 1983.

206. Andrews, C.P., et al. Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest. 80:254, 1981.

207. Montgomery, B.A., et al. Causes of mortality in patients with the adult respiratory distress syndrome. Amer.Rev.Resp.Dis. 132:485, 1985.