Resolution of Pulmonary Edema
New Insights

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *The focus on pulmonary edema is usually on the mechanisms of formation. Little attention is paid to the other determinant of excess lung water, the clearance of edema fluid from the lung. The resolution of pulmonary edema will be discussed by Michael A. Matthay, MD, a member of the faculty of the Departments of Medicine and Anesthesia at UCSF and a member of the senior staff and of the Cardiovascular Research Institute, where his experimental and clinical research has included studies of the ion and protein transport properties of the alveolar epithelium.*

MICHAEL A. MATTHAY, MD†: The primary scientific objective of this work‡ has been to determine the mechanisms responsible for the clearance of liquid and protein from the air spaces of the lung. This scientific objective complements our clinical objective to develop a better understanding of the resolution phase of pulmonary edema.

By way of brief review, recall that physiologically there are two types of pulmonary edema: hydrostatic edema and increased permeability edema.[1-3] Hydrostatic pulmonary edema develops because of elevated pressure in the microcirculation of the lung, usually due to left-sided heart failure. About two thirds of clinical cases of pulmonary edema are related to elevated hydrostatic pressures in the pulmonary circulation. The other third of the cases are related to an increase in the permeability of the pulmonary capillaries from sepsis, gastric aspiration, and other causes of acute lung injury.

To appreciate the morphologic basis for the development of edema in the lung, it is necessary to recall the normal structure of the alveolar-capillary unit. The alveolar capillaries in the lung are surrounded by an interstitial space, which is separated from the air spaces by the alveolar epithelial barrier (Figure 1). Under normal conditions, some fluid and a small amount of protein filter into the interstitium from the alveolar capillaries through small gap junctions in the endothelium. The gap junctions between the cells of the normal alveolar epithelium are much tighter (Figure 1). This makes good sense teleologically because it is important that the air spaces remain dry for the lung to carry out its primary function of exchanging gas. Therefore, the alveolar epithelium should offer substantial resistance to the passive movement of liquid and protein into the alveoli.

In either type of pulmonary edema, an increased quantity of fluid moves from the vascular to the interstitial space of the lung. About 500 ml of edema fluid can collect in the interstitium of the lung before the interstitial pressure is high enough for edema fluid to break through the epithelium and flood the air spaces.[1,3]

Pulmonary edema fluid contains both liquid and protein. The initial specimen of pulmonary edema fluid from patients with cardiac failure has a protein concentration of about 30 grams per liter; in patients with increased permeability pulmonary edema, the protein concentration is usually higher, 40 to 60 grams per liter.[4,5] The distinction between hydrostatic and increased permeability pulmonary edema can usually be made by analyzing the ratio of the protein concentration in pulmonary edema to that in plasma.[4-6] If the ratio is 0.65 or lower, the edema fluid is a transudate, diagnostic of hydrostatic edema; if the ratio is 0.75 or higher, the fluid probably reflects increased permeability, although the edema fluid specimen must be obtained before resolution has begun (see later discussion of this issue). If the ratio is between 0.65 and 0.75, the type of pulmonary edema is indeterminate. The cellular content of the edema fluid depends on associated conditions, such as hemorrhage or inflammation. There are always some erythrocytes and a few monocytes in hydrostatic edema fluid; in most cases of increased permeability edema, the number of neutrophils is greater than in hydrostatic pulmonary edema.[7]

Resolution of Pulmonary Edema

Experimental Studies

To analyze the resolution phase of pulmonary edema, it is important to recognize that there are two extravascular

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ABBREVIATIONS USED IN TEXT

PEEP = positive end-expiratory pressure
UCSF = University of California, San Francisco

spaces in which edema fluid can accumulate in the lung: the interstitium and the air spaces. When edema fluid is confined to the lung interstitium, the effects on gas exchange are usually minor. When it floods the air spaces, however, substantial gas-exchange abnormalities develop. For example, when the left atrial pressure is raised to a modest level—16 to 22 mm of mercury—only interstitial edema develops. The edema fluid collects in cuffs primarily around pulmonary arteries and airways (Figure 2).[8] As mentioned, the distensible interstitial space can absorb a considerable quantity of edema fluid before the interstitial edema moves into the air spaces. A chest radiograph shows increased interstitial markings such as Kerley's lines.[9,10]

Removing edema fluid from the lung interstitium is not a major problem. A number of radiographic studies have indicated that interstitial edema resolves within 12 to 24 hours.[9] The edema fluid can be removed through several pathways including the lung lymphatics and the pulmonary or bronchial circulation. Also, the pleural space has recently been shown to be an important pathway for clearing edema fluid from the lung. Wiener-Kronish and Broaddus and co-workers have shown in both experimental and clinical studies that as much as 25% of edema fluid will move from the lung into the pleural space in both hydrostatic and increased permeability edema.[11,12]

The development of alveolar edema results in much more extensive pulmonary edema, which can be appreciated radiographically.[13] Moreover, removing edema fluid from the air spaces of the lung presents a substantially different problem from clearing it from the interstitium. The major reason for this difference is the presence of the tight epithelial barrier, which normally has a low permeability to both macromolecules and solutes.[14-16] Thus, the removal of edema fluid from the alveoli of the lung first requires that the fluid move across the tight epithelial barrier before it reaches the lung interstitium where, as mentioned, there are several readily available clearance pathways.

In our initial studies, we developed an experimental model that reproduced some of the clinical features of pulmonary edema. Because edema fluid is composed of both a liquid and a protein fraction, we designed the experiments to study alveolar liquid and alveolar protein clearance simultaneously. Therefore, we instilled autologous serum (2 to 3 ml per kg of body weight) into the distal air spaces of one lung.[16,17] This was done with a bronchoscope in large animals (sheep or dogs) and with a catheter in small animals (rabbits and rats). In the larger animals, the instilled volume was about 100 ml of serum into one lower lobe. The serum was stained with Evans blue so that at the end of the experiment we could determine that it was localized to one lower lobe. We also added to the instilled serum ^{125}I-labeled albumin to provide a quantitative marker for the instilled alveo-

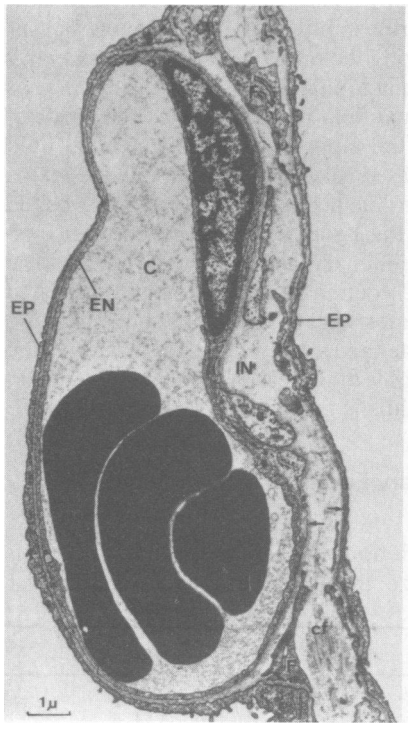

Figure 1.—Electron micrograph of a cross-section of an alveolar capillary **(C)** from human lung. Blood cells are suspended in the interalveolar septum between two alveolar spaces. The alveolar epithelium **(EP)** is the barrier that separates the air spaces from the interstitium **(IN)**. Fluid and protein exchange probably occurs through small gaps between the endothelial cells **(EN)** in the alveolar capillaries. Connective tissue fibers are found in the interstitium, where the basal laminae **(arrows)** of the epithelium and endothelium are separated (reproduced with permission from Fishman et al[2(p4)]). cf = fibroblast cell

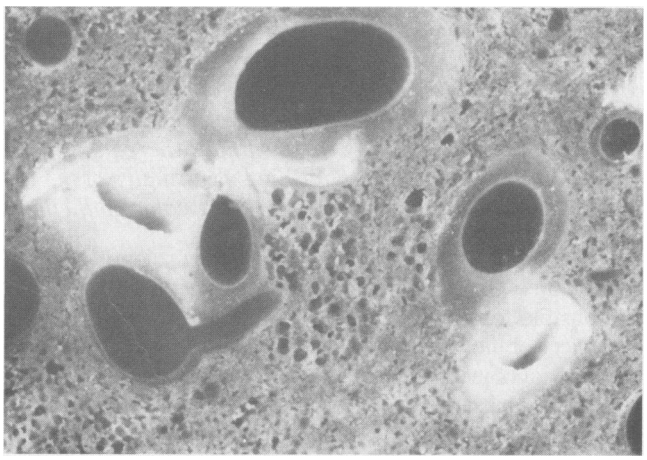

Figure 2.—The photograph shows a specimen of frozen sheep lung. In this experimental study, the left atrial pressure was elevated to 20 cm of water for 4 hours. The result is interstitial pulmonary edema with perivascular fluid cuffs around pulmonary arteries and small airways. There are some lymphatics visible in the fluid cuffs also (reproduced with permission from George[8(p442)]).

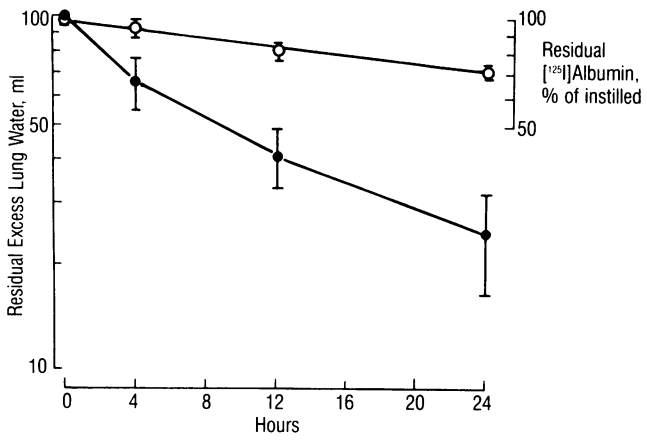

Figure 3.—The removal rate of 100 ml of excess water and ^{125}I-labeled albumin over 24 hours is plotted logarithmically. Solid circles represent the means ± the standard deviation (SD) of residual excess water left in serum-instilled lobe at 4, 12, and 24 hours. Open circles represent the means ± SD of residual [^{125}I]albumin in experimental lung expressed as a percent of the total instilled [^{125}I]albumin at 4, 12, and 24 hours (reproduced with permission from Matthay et al[17]).

lar protein that would enable us to determine how much of the protein tracer remained in the lung at the end of the study and how much entered the lung lymph and plasma during the study. The experiments lasted from 1 to 24 hours. At the end of each experiment, the lungs were removed and a catheter was wedged through the airways into the distal air spaces of the serum-instilled lung to obtain a specimen of the residual alveolar fluid. The total protein concentration, the radioactivity, and the cell count of that specimen were measured. Biopsy specimens were taken for histologic study, and the lungs were then homogenized separately; the excess liquid volume remaining in the serum-instilled lung was determined gravimetrically.

Our early studies in sheep showed that excess liquid is cleared from the air spaces at a much faster rate than is protein.[16,17] About 75% of the liquid volume but only 25% of the protein was removed from the lung by 24 hours (Figure 3).[17] The differential clearance rates for liquid and protein were related to the slower clearance of protein across the tight alveolar epithelial barrier. In fact, we found that the protein concentration of the serum that was instilled into the air spaces of one lung progressively increased to levels well above the plasma protein concentration.[16]

A substantial rise in the alveolar protein concentration was evident after only four hours. In one series of experiments, we found that by four hours after the instillation of 100 ml of autologous serum into one lower lobe, a third of the liquid volume had been removed from the lung and the protein concentration increased from 63 to 84 grams per liter (Table 1). Thus, the alveolar protein concentration was about 20 grams per liter higher than the plasma protein concentration. This observation led us to propose the hypothesis that there must be an active ion transport system removing liquid from the air spaces.[16]

Further support for this hypothesis was obtained when the 4-hour studies were extended to 12 and 24 hours.[17] Over the longer time periods, there was a progressive clearance of the alveolar liquid so that the instilled protein in the serum in the air spaces increased to 129 grams per liter by 24 hours (Table 1). Thus, the protein osmotic pressure of the alveolar fluid was very high. This was further evidence that there must be an active ion transport mechanism involved in removing liquid from the air spaces of the lungs.

To examine our hypothesis, we tested various specific sodium and chloride channel inhibitors. We used furosemide, for example, which inhibits sodium chloride cotransport, but this agent had no effect at the alveolar epithelial level.[17] Using amiloride, however, had a substantial effect. Amiloride blocks the uptake of sodium across the apical epithelium. In our sheep studies, amiloride inhibited about 50% of the clearance.[18,19] Other investigators showed that type II alveolar epithelial cells formed fluid domes when they were cultured in monolayers. The formation of these domes could be inhibited by removing sodium from the medium or by administering amiloride.[20,21]

In the cell culture studies, some investigators found that if a β-adrenergic agonist was applied, dome formation was greater.[22] Therefore, we did a series of studies in sheep in which we added terbutaline (a β_2-adrenergic agonist) to the serum that was instilled into the air spaces.[23] The terbutaline increased alveolar and lung liquid clearance dramatically. This effect did not depend on terbutaline-induced changes in hemodynamics, blood flow, or lung lymph flow.[23] Also, amiloride blocked 90% of terbutaline's effect. Thus, we concluded that in sheep, β-agonists dramatically increased alveolar liquid clearance by augmenting sodium transport from the air spaces. Subsequently terbutaline was found to also increase alveolar liquid clearance in dogs.[24]

As mentioned, amiloride inhibited 50% of basal liquid clearance in sheep, and in subsequent studies, we found that this agent blocked 75% of basal liquid clearance in rabbits.[25] What about the remaining 25% to 50% of alveolar liquid clearance? Could it be that the remaining fraction of clearance depends on a hydrostatic pressure gradient generated by ventilation? In earlier studies, the rate of alveolar liquid clearance in sheep and dogs was found to be the same whether the sheep were ventilated with positive pressure or were breathing spontaneously.[16,17,24] We had not ruled out the possibility that passive transmission of the pressure across the epithelium might also contribute to alveolar liquid clearance.

To answer that question, we did an additional study in sheep. Serum (3 ml per kg) was instilled into the left lung and then the left bronchus clamped so that the lung would not be ventilated. The sheep was ventilated by the right lung only. Even in the absence of ventilation, alveolar and lung liquid clearance from the left lung over four hours was normal.[26] This finding provided additional evidence that all of alveolar epithelial solute and liquid clearance depends on an active ion transport process.

Overall, we have studied three species: dogs, sheep, and rabbits. All have a similar pattern of alveolar liquid clearance with an increase in alveolar protein concentration to levels well above the plasma protein concentration, but the rate of alveolar liquid clearance varies among species. Dogs have the slowest basal clearance, sheep have an intermediate rate, and rabbits have a fast rate of alveolar liquid clearance (Table 2). The mechanism for this species difference may be related to the number or the activity of the sodium transport channels in the epithelium.

TABLE 1.—*Alveolar Liquid Clearance in Sheep as Reflected by Progressive Concentration of Protein in the Air Spaces of the Lung**

Time, h	Alveolar Protein Concentration, grams/liter		Lung Liquid Clearance, % of Instilled§
	Initial†	Final‡	
4	63±6	84±6	33.2
12	59±4	102±12	59.2
24	64±6	129±19	75.9

*Data are shown as mean ± standard deviation.
†The initial alveolar protein refers to the protein concentration of the instilled serum (3 ml/kg).
‡The increase in concentration of protein in the air spaces can be used to estimate the alveolar liquid clearance by a simple proportion calculation because the instilled volume and the initial and final alveolar protein concentration are known (Berthiaume et al[23,24]).
§The clearance of liquid from the lung was calculated by the gravimetric method (Matthay et al[16,17]).

TABLE 2.—*Estimated Basal Rates of Alveolar Liquid Clearance in Dogs, Sheep, and Rabbits*

Species	Half-life for Alveolar Liquid Clearance, h	Source
Dogs	18	Berthiaume et al, 1988[24]
Sheep	9	Matthay et al, 1985[17]
Rabbits	6	Smedira et al, 1991[25]

Clinical Studies

In recent clinical studies, Wiener-Kronish and I have studied the resolution of pulmonary edema in humans.[27] The primary objective of these studies was to test the hypothesis that alveolar protein concentration would increase as alveolar edema was cleared from the air spaces of the lung. If we established that this was the pattern for the resolution of alveolar edema in humans, this information would provide further evidence for the hypothesis that active ion transport was important in humans as a critical mechanism for the clearance of excess alveolar fluid.

All patients who had sufficiently severe pulmonary edema to require mechanical ventilation were entered in the study. A specimen of pulmonary edema fluid was taken by suctioning through the endotracheal tube with a standard 14-gauge French catheter wedged into the distal bronchi within 15 minutes after endotracheal intubation. At the same time, a specimen of plasma was obtained for protein concentration, arterial blood gas measurements were done, and a chest radiograph was taken. A subsequent edema specimen was obtained if the patient's oxygenation improved as indicated by a decrease in the alveolar-arterial oxygen pressure difference by 50 mm of mercury; if the patient's oxygenation worsened as indicated by an increase in the alveolar-arterial oxygen pressure difference by 50 mm of mercury or more; or if there was a need to increase positive end-expiratory pressure (PEEP) by 3 cm of water or more to maintain oxygenation. If there was no change in oxygenation or the PEEP level, then a final edema fluid specimen was obtained at 12 hours.

A total of 34 patients were enrolled in the study.[27] Of these, 24 improved clinically as defined by better oxygenation and a decrease in edema on the chest film. Of these 24 patients, 15 had hydrostatic edema and 9 had increased permeability edema. Ten patients did not clinically improve. The initial alveolar-arterial oxygen pressure difference was similar in the two groups (Table 3). The final specimen in the patients with clinical improvement was obtained, as indicated, when the alveolar-arterial oxygen pressure difference had improved. The time interval for the final edema fluid specimen was similar in all patients. In contrast, of the ten patients with no improvement, seven had increased permeability and three had hydrostatic edema. Their initial alveolar-arterial oxygen differences were similar at the outset to those of the patients who improved (Table 3).

Chest radiographs correlated with the oxygenation data in 90% of the patients. Specifically, in 21 of the 24 patients whose oxygenation improved, the chest radiograph taken at the time of the second edema fluid specimen showed less pulmonary edema (Figure 4).

Of the 15 patients with hydrostatic pulmonary edema who improved clinically, the edema fluid protein concentration increased from the initial value in every patient, with no change in the plasma protein level (Table 4). The three patients with hydrostatic edema who did not improve had no change in their edema fluid protein concentration. Thus, the resolution of alveolar edema in hydrostatic alveolar edema was associated with an increase in the edema fluid protein concentration.

What happened to the nine patients with increased permeability who improved clinically? All of these patients had an increase in their edema fluid protein concentration to a mean level of 68 grams per liter (Table 4). In several of the patients, the final edema fluid protein concentration exceeded the plasma protein level. This result matched well with our experimental studies, which had shown that alveolar protein levels would rise well above the plasma protein level.[11,16,17,23,24] The seven patients with increased permeability edema who did not improve had no change in the alveolar edema protein concentration between the initial and follow-up specimens.[27]

TABLE 3.—*Alveolar-Arterial Oxygen Pressure Difference in Patients With Pulmonary Edema*†*

Classification of Edema	Patients, No.	Alveolar-Arterial Oxygen Difference, mm of mercury		Time Interval, h
		Initial	Final	
Clinical Improvement				
Hydrostatic	15	545±74	366±124‡	4.5±2.9
Increased permeability	9	553±40	368±112‡	6.8±5.1
No Clinical Improvement				
Hydrostatic	3	588±23	616±22	5.3±5.8
Increased permeability	7	518±84	538±95	5.4±4.1

*From Matthay and Wiener-Kronish.[27]
†Data are shown as the mean ± standard deviation.
‡$P<.01$ when comparing the final with the initial alveolar-arterial oxygen difference.

TABLE 4.—*Rates of Alveolar Fluid Clearance in Hydrostatic Versus Increased Permeability Pulmonary Edema in Patients With Clinical Improvement**

Classification of Edema	Patients, No.	Total Protein Concentration, grams/liter†		Concentration (%) Over Baseline§ Rate of Resolution, %/h	
		Initial	Final	Range	Mean†
Hydrostatic	15	33±10	48±23‡	3-39	12±10
Increased permeability	9	47±9	68±16‡	3-24	11±8

*From Matthay and Wiener-Kronish.[27]
†Data are shown as the mean ± standard deviation.
‡$P<.01$ compared with the initial edema fluid protein concentration.
§Concentration of the total protein in the final edema specimen compared with the initial edema specimen divided by the time interval in hours between the specimens provides an estimate of alveolar fluid clearance (Sprung et al,[6] Matthay et al[16,18]).

Thus, these results confirmed our basic hypothesis: as alveolar liquid was cleared from the air spaces, the edema fluid protein concentration would rise. As a specific example, consider the data on a patient who initially presented with a protein concentration in pulmonary edema fluid of 44 grams per liter and a plasma protein level of 70 grams per liter. He had hydrostatic edema (ratio, 0.64). The measured protein osmotic pressure on the initial pulmonary edema fluid was 20 mm of mercury. Four hours later, when the patient's oxygenation was improved and the chest radiograph showed less pulmonary edema, a follow-up edema fluid specimen had a protein concentration of 111 grams per liter, with a plasma protein of 70 grams per liter. The measured protein osmotic pressure of the edema fluid was 72 mm of mercury. Thus, these data showed that in humans, alveolar protein can concentrate to high levels and that there could be a large protein osmotic pressure gradient from the air spaces to the vascular bed.

This clinical study also gave us an opportunity to estimate the rate of alveolar liquid clearance in patients who had resolving hydrostatic or resolving permeability edema. We did not anticipate when we began the study that so many patients with increased permeability edema would have such rapid clearing. We thought that the resolution of pulmonary edema in humans would have to be studied primarily in patients with hydrostatic (cardiogenic) pulmonary edema because permeability edema would resolve too slowly for a short-term (12-hour) clinical study. But, as the data indicate, at least half the patients with increased permeability edema had their pulmonary edema resolve at a rate similar to that found in patients with hydrostatic edema (Table 4). Among those whose edema resolved, the mean rate of clearance was 12% per hour in the hydrostatic group versus 11% per hour in the increased permeability group.

We estimated the rate of alveolar liquid clearance from the measurement of changes in the protein concentration in edema fluid obtained from the air spaces in humans and compared these data with those in the other species we have studied (Table 2). From this estimate, it appears that humans have a rapid rate of alveolar liquid clearance. Alveolar liquid clearance in dogs, although slow, can be stimulated with β-agonist therapy; the intermediate rate of alveolar liquid clearance in sheep also increases with β-adrenergic agonist therapy. The basal clearance in rabbits does not respond to the use of terbutaline. We do not know whether alveolar fluid clearance in humans can be accelerated with β-adrenergic agonists.

Alveolar Epithelial Barrier

Prognostic Implications

As our clinical study progressed, it became clear that there were at least two populations of patients with increased permeability pulmonary edema, or the adult respiratory distress syndrome.[27] Group A included the nine patients who had an increase in edema fluid to plasma protein ratio of 10% or more in sequential specimens compared with the baseline value (Figure 5). Group B included the seven patients who had no change in their ratio of baseline edema fluid to plasma protein concentration throughout the course of the study, which indicated that the net quantity of edema in the air spaces was not decreasing (Figure 5).

In group A, mortality was only 22% (2 of 9). In fact, even the two patients who eventually died had recovered from their acute respiratory failure. One died of pulmonary embolism weeks later, and the other died of advanced carcinoma. Thus, all nine of these patients actually recovered from their acute respiratory failure and increased permeability pulmonary edema. In contrast, mortality was 71% in the group B patients (5 of 7). Of the two who lived, both required mechanical ventilation, one for 90 days and the other for 30 days. Although we studied only a small group, our findings suggest that determining the edema fluid protein concentra-

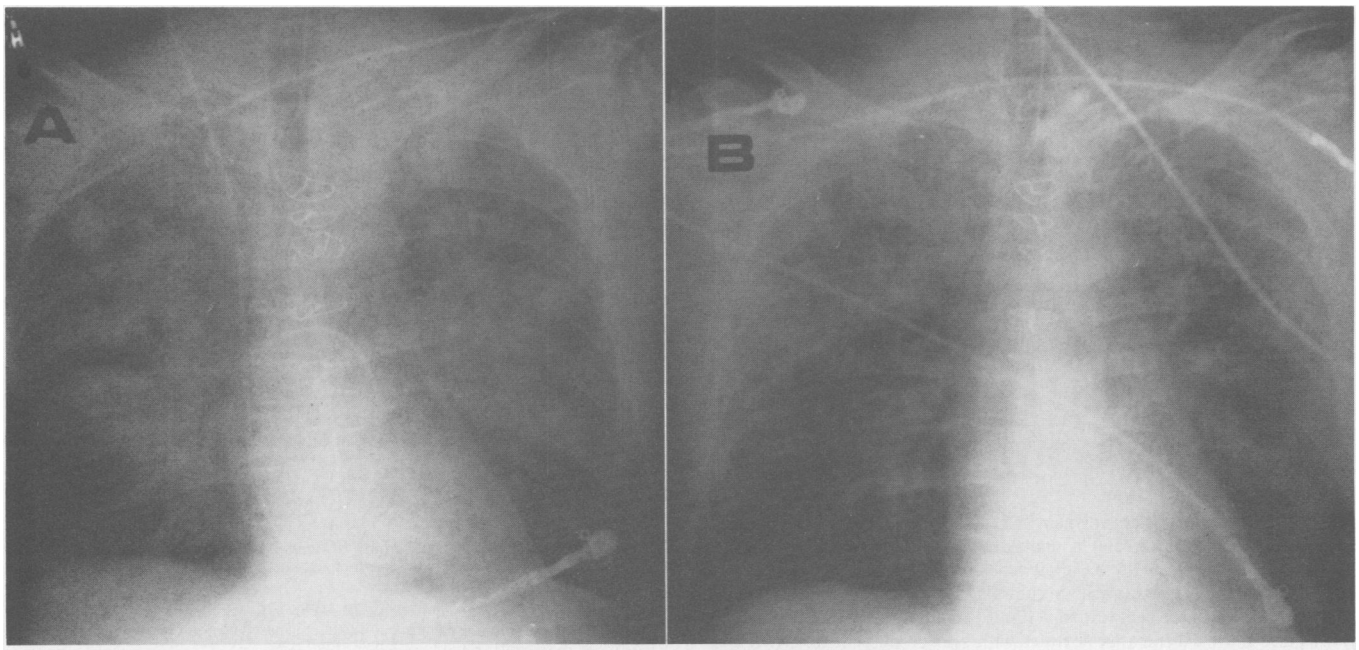

Figure 4.—A, Anteroposterior portable chest radiograph was taken of a patient following cardiopulmonary bypass in whom increased permeability pulmonary edema developed. The pulmonary arterial wedge pressure was 9 mm of mercury. The initial pulmonary edema fluid:plasma protein ratio was 0.85 at the time of this chest radiograph. **B,** Four hours later, a repeat chest radiograph was taken when the alveolar-arterial oxygen difference had decreased and a second pulmonary edema fluid: plasma protein concentration ratio had increased to 1.2. Note that the extent of pulmonary edema is significantly less on this second chest radiograph.

tion in the first 12 hours after acute lung injury might be useful as a prognostic indicator of the severity of acute lung injury.

Were there other factors that influenced this outcome? The pulmonary arterial wedge pressure did not differ between the two groups. Thus, the difference between the groups was not related to differences in cardiac function or intravascular pressures. Also, the initial PEEP levels were the same in the groups, although the final level of PEEP was higher in group B, reflecting the need for higher levels of PEEP to support oxygenation.

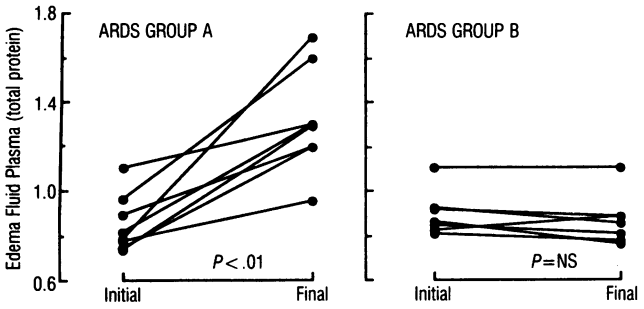

Figure 5.—Individual data points are shown for the initial and final pulmonary fluid-to-plasma total protein concentration ratio in 9 patients with the adult respiratory distress syndrome (ARDS) who clinically improved (group A) compared with the 7 ARDS patients who did not clinically improve (group B). The time interval between the initial and final specimen was similar between the group A (6.8 ± 5.1 hours) and the group B (5.4 ± 4.1 hours) patients (from Matthay and Wiener-Kronish,[27] reprinted with permission from the American Thoracic Society).

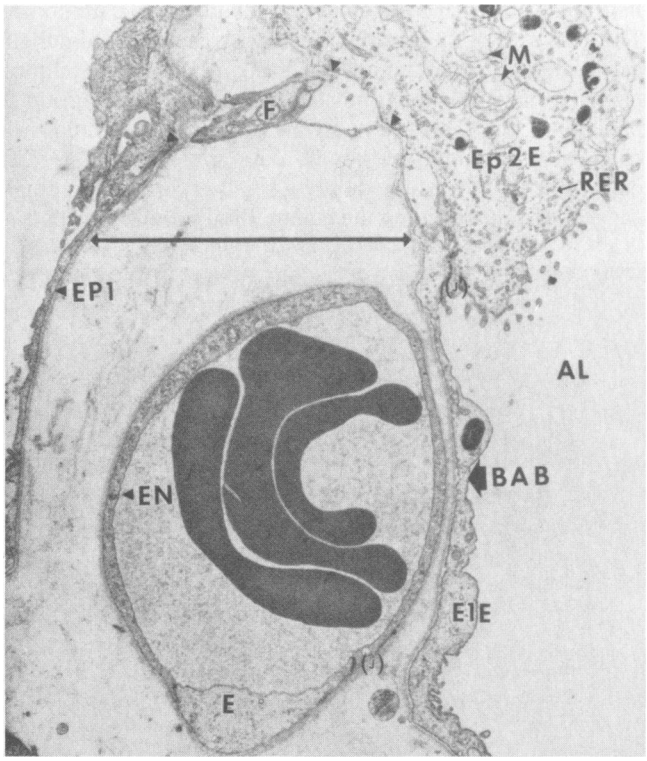

Figure 6.—Human interstitial edema with cellular injury is shown. The connective tissue space **(long arrow)** is markedly swollen, whereas the blood-air barrier **(BAB)** is normal. Normal gray capillary endothelial **(EN)** and type I epithelial cells **(EP1)** serve as built-in controls for swollen endothelial **(E)**, type I epithelial **(E1E)**, and type II epithelial **(Ep2E)** edematous cells. Epithelial type II cells also show degenerative features with swollen mitochondria **(M)** and degranulating rough endoplasmic reticulum **(RER)**. Interstitial fibrocyte **(F)** anchors the epithelial basement membranes **(arrow heads)**. J and J' are endothelial and epithelial junctions (from Fishman and Renkin,[2(p4)] reprinted with permission from the American Physiological Society). AL = alveolus

What was the distribution of clinical disorders associated with the adult respiratory distress syndrome in these groups? Sepsis was more frequently associated with acute lung injury in the group B patients. In group A, two patients had sepsis, two had a blood product reaction, two had complications after a cardiopulmonary bypass, one had gastric aspiration, and two had overdosed drugs. Sepsis has been reported to be a more lethal and severe form of acute lung injury.[28]

In summary, sequential specimens of pulmonary edema fluid in the first 12 hours after endotracheal intubation appear to identify two groups of patients with acute lung injury. In one group, alveolar epithelial barrier function appears to be relatively intact whereas in the other group lung injury appears to be more severe with damage to both the endothelium and epithelium. Mortality is apparently lower in the patients with intact alveolar epithelial barrier function. In fact, in the classic study by Bachofen and Weibel of patients who died of acute lung injury following sepsis, all patients had evidence of both lung endothelial and alveolar epithelial injury.[29] Other investigators have also reported alveolar epithelial injury in patients who have died in the acute phase of the adult respiratory distress syndrome (Figure 6).[30]

Conclusions

Both experimental and clinical studies support the conclusion that active ion (sodium) transport is the primary mechanism responsible for the clearance of excess liquid or edema fluid from the air spaces of the lung. Second, the integrity of the alveolar epithelium is an important factor in determining the extent of acute lung injury and survival in patients with acute lung injury. More experimental studies are needed to identify mechanisms that cause injury to the alveolar epithelium, a critical barrier in determining the extent of acute lung injury.

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