Pulmonary Edema due to Increased
Microvascular Permeability to Fluid and
Protein

NORMAN C. STAUB

THE USUAL clinical designation of pulmonary edema as either cardiogenic or noncardiogenic implies a pathophysiology that is not necessarily true and, in the case of noncardiogenic edema, is singularly uninformative. A better classification would be one based upon the two major variables in the equation for transvascular fluid flow (Starling's equation), namely,

\[ \text{Net fluid flow} = \text{conductance} \times \text{driving pressure} \]

or, in symbols,

\[ \dot{Q}_f = K(P_{mv} - P_{pmv}) - K_\alpha (\Pi_{mv} - \Pi_{pmv}) \]  (1)

where \( \dot{Q}_f \) is the net transvascular fluid flow, \( K \) is the fluid filtration coefficient, \( P \) is the hydrostatic pressure in the microvascular* lumen (mv) and perimicrovascular* interstitial fluid (pmv), respectively; \( \alpha \) is a weighted plasma protein reflection coefficient which determines the "effective" transvascular protein osmotic pressure difference; and \( \Pi \) is the protein osmotic pressure in the plasma (mv) and perimicrovascular (pmv) compartments, respectively.

According to Equation 1, the two major types of edema are that due to increased driving pressure (high pressure edema) and that due to altered integrity of the microvascular membrane (permeability edema).

**High pressure edema** may be of cardiac origin (increased microvascular hydrostatic pressure due to left atrial hypertension), but it also may occur when cardiac function is normal as in overexpansion of extracellular volume by crystalloid fluid infusions¹ (increased pulmonary microvascular hydrostatic pressure and decreased microvascular protein osmotic pressure), or by decreased perimicrovascular interstitial fluid pressure (such as may result from sudden reexpansion of a collapsed lung by excessive negative pleural pressure).

The term, permeability edema, requires further explanation. It is meant to signify that an increase has occurred in the transendothelial conductance for water (represented by the filtration coefficient, \( K \)), and that a decrease has occurred in the microvascular barrier restriction to the flow of plasma proteins (as represented by the reflection coefficient, \( \alpha \)).

Most quantitative experimental work on pulmonary edema²⁻⁴ has been on the high pressure variety because it is so much easier to produce and control than is the altered permeability variety. Recent reviews⁵⁻⁶ have tended to dwell on the high pressure form of edema, although a recent symposium⁷ was devoted entirely to permeability edema.

This Brief Review is warranted in part by the rapid progress that is occurring in our understanding of altered microvascular endothelial permeability to water and protein, and in part by the increased incidence and awareness of this form of edema in man.⁵⁻⁷

The Definition of Permeability Edema

Strictly speaking, the Starling equation alone (Equation 1) is not sufficient to describe permeability edema. A parallel equation for protein flux is necessary, namely,

\[ \dot{Q}_s = \omega(\Pi_{mv} - \Pi_{pmv}) + (1 - \alpha) \bar{C}_S \dot{Q}_f \]  (2)

where \( \dot{Q}_s \) is the net protein flux; \( \omega \) is the true permeability coefficient for protein diffusion; and \( \bar{C}_S \) is the average concentration of protein across the microvascular membrane.

Equations 1 and 2 contain three parameters: \( K, \alpha, \omega \). The first is a measure of the microvascular barrier's hydraulic conductivity to water. The other two are mea-
sures of the barrier’s restriction to the convective and diffusive flux of protein, respectively. Permeability edema is characterized by changes in these three parameters.

Is it possible to separate water flux from protein flux? Can there be an increased water flux permeability edema separate from an increased protein permeability edema? In theory, yes.

In devising models that will represent fluid and protein flux successfully, we rely on multiple equivalent pores. It is possible to separate, at least partially, protein flow from water flow. The models contain pores of different sizes, some of which are so small that only water and electrolytes can pass through them. They are completely impermeable to protein. If we increase the number of these very small pores, we increase the filtration coefficient, K, without much increase in protein flux. An edema of this kind would be detected by an increased lung lymph flow or lung water content, but the protein concentration of these fluids would be reduced relative to plasma. In other words, the edema fluid would be similar to that obtained in high pressure edema except that the sum of pressures (Equation 1) would be decreased, not elevated. An edema of purely increased protein permeability is also possible, but only if there is a nonhydraulic pathway for protein flow, such as endothelial vesicles.

As a practical matter, these forms of edema do not exist. To my knowledge, all known permeability edemas cause an increase both in water and protein flow.

A further consideration is that both water and protein flux ought to be directly related to vascular surface area. Thus, halving or doubling endothelial surface area should reduce water and protein fluxes by 50% or increase them by 100%. Changes in vascular surface area are not to be called permeability edema. For example, suppose the right and left lung, considered individually, are equally permeable to water and protein. Their combined permeability is not twice that of either one alone, since the increased fluid and protein fluxes are entirely due to an increased surface area.

Permeability edema is identified experimentally and clinically by an increase in lung lymph flow or lung water content, both of which contain plasma proteins at concentrations higher than expected for the known driving pressures.

Very recently investigators have begun to identify increased permeability in the lung by changes in the rate of equilibration of tracer proteins.

Causes of Permeability Edema

The list of specific agents that will lead to permeability edema is probably open-ended. A lengthy list has been published and new agents are reported frequently.

Typical experimental examples of permeability edema are those induced by alphanaphthyl thiourea in rats, alloxan and oleic acid in dogs, and pseudomonas bacteremia in sheep. Clinical examples probably include high altitude pulmonary edema, neurogenic pulmonary edema, the shock lung group, microembolism syndrome, and various drug idiosyncrasies (heroin, salicylates).

Table 1 summarizes the protein concentration in lung edema fluid or lung lymph relative to plasma in what are believed to be some permeability edemas in man and experimental animals. The protein concentrations in the lung fluids range between 72 and 96% of the simultaneously measured plasma concentration. In experimental animals, the protein concentration of lung lymph normally averages about 65% of the simultaneously measured plasma value, but the range is fairly broad (50-80%). The protein concentrations shown in Table 1 are on the high side of the predicted normal or even above it. All these edemas conform to the required definition, that is, a demonstrated large increase in lung fluid filtration coupled to a large increase in protein flow out of the microvascular bed.

The identity of lung lymph protein concentration to that of perimicrovascular fluid has been demonstrated in sheep with experimental pulmonary edema. In the normal lung, the perimicrovascular interstitial fluid is not available for direct comparison with lymph, but most investigators assume their identity (see reference 6 for an extended discussion).

Normal Intercellular Junctions

The physical description of the fine structure of intercellular junctions has progressed spectacularly since Claude and Goodenough’s freeze-fracture study in 1973. The lung’s endothelial and epithelial junctions have been carefully examined by Schneeberger and Karnovsky and Inoue et al.

The zonulae occludentes in the microvasculature are rather poorly developed and correspond to “leaky” junctions. Schneeberger makes a further distinction. She suggests an increasing leakiness from arterial to venular ends of the microvessels.

At the opposite extreme, we know very little about how intercellular adherence is regulated. Why are alveolar epithelial junctions “tighter” than endothelial ones? Do endothelial cells sense the rate of fluid and protein flow into the perimicrovascular interstitium?

As far as I know, microvascular permeability never has been reported to be less than normal. This suggests that the normal attachment between cells is the tightest that can be achieved. Why then is there a gradient of permeability and junctional morphology from arterioles to ven-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary leak</td>
<td>Human</td>
</tr>
<tr>
<td>Heroin</td>
<td>Human</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>Human</td>
</tr>
<tr>
<td>Non-cardiogenic</td>
<td>Human</td>
</tr>
<tr>
<td>Alloxan</td>
<td>Dog</td>
</tr>
<tr>
<td>Pseudomonas bacteremia</td>
<td>Sheep</td>
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Table 1. Protein Composition of Lung Fluids in Permeability Edema

<table>
<thead>
<tr>
<th>Species</th>
<th>Condition</th>
<th>Plasma</th>
<th>Edema fluid</th>
<th>Lung lymph</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Human</td>
<td></td>
<td>4.0</td>
<td>3.6</td>
<td>3.6</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0</td>
<td>5.8</td>
<td>5.8</td>
<td>24</td>
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<tr>
<td></td>
<td></td>
<td>6.8</td>
<td>5.8</td>
<td>5.8</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.8</td>
<td>4.9</td>
<td>4.9</td>
<td>26</td>
</tr>
<tr>
<td>B. Dog</td>
<td></td>
<td>4.9</td>
<td>4.4</td>
<td>4.4</td>
<td>27</td>
</tr>
<tr>
<td>C. Sheep</td>
<td>Pseudomonas bacteremia</td>
<td>5.7</td>
<td>4.6</td>
<td>4.1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Concentration in g/dl.
† Terms are authors’ euphemisms for increased permeability edema.
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PULMONARY EDEMA/Staub

ules?29,32 Is the “tightness” pressure sensitive? That may be a partial explanation for endothelium but it does not explain epithelial tight junctions. If we knew how normal microvascular intercellular junctions are maintained, we would be closer to being able to restore endothelial integrity toward normal when it is altered.

Mechanisms of Permeability Edema

Before discussing specific mechanisms, I will review my concept of the nature of the injury causing permeability edema. I believe that the final common pathway is a variable loosening of the junctions between endothelial cells. However, the route of attack (for example, directly at the junction; indirectly through cellular injury) varies so that it is unlikely there will be a single treatment that reverses permeability edema.

The derangement of junctional architecture need only be modest in order to produce a flood of fluid and protein into the lung’s interstitium.34 This view is, perhaps, somewhat at variance with classical pathology, from which we have been led to believe that severe microvascular endothelial injury is needed to produce significant increased permeability edema.

The early ultrastructural investigations of Schultz33 and others.34,35 showed severe microvascular endothelial and alveolar epithelial damage in permeability edema characterized by cell swelling, vacuolization, bleb formation, and general membrane dissolution. The recent studies of Cottrell and associates36 seemed to support this notion, although others have not found such wholesale destruction.37-39 These latter reports are more in tune with clinical experience wherein permeability edema may be a limited and reversible process.34

In my opinion, the most significant pathological analysis of permeability edema is that by Hovig et al.40 They produced acute and massive permeability edema in isolated, perfused rabbit lungs, but by electron microscopy they could not find any obvious structural changes in the microvascular endothelium, including the intercellular junctions. Meyrick et al.41 have confirmed their results.

We investigated a physiological model of permeability edema caused by the intravenous infusion of Pseudomonas bacteria into unanesthetized sheep. This led to marked increases in the flow of lung lymph that was rich in protein. Two of our first seven sheep died in acute pulmonary edema. The others recovered to their baseline condition within 24-72 hours.10

When we used our multiple equivalent pore model10 to explain the animals’ condition during the steady state period of maximum increased microvascular permeability, we discovered that only modest loosening of the intercellular junctions was required. In fact, the predicted changes in small and intermediate pore sizes would be difficult to detect even by quantitative electron microscopy.

Specific Mechanisms

Chemicals

There are two clearly defined chemical causes of permeability edema. Nicolaysen42 used chelating compounds to selectively remove calcium from the perfusing fluid and interstitium of isolated rabbit lungs. Increased permeability edema began within a few minutes and was rapidly reversed when he added calcium to the perfusate. The very low levels of calcium necessary are incompatible with life in intact animals and man; nevertheless, it is important as a paradigm for direct action on the intercellular junction.43,44

Pietra and co-workers45 established that histamine affects vascular permeability in the lung. The introduced large local concentrations into dog lungs and demonstrated colloidal carbon accumulation and “gap” formation confined to bronchial venules. This is similar to histamine’s action on other systemic venules.46 However gap formation is believed to be a transient phenomenon.46

Brigham and Owen47 found that infusion of histamine [4 µg/(min × kg)] increased lung vascular permeability for as long as 4 hours. They found histamine to be more effective when infused into the pulmonary artery than into the left atrium, and they suggested that the principal sustained action was on the pulmonary vascular endothelium. A clear distinction between sites of action in the bronchial or pulmonary circulation is difficult because histamine is readily diffusible within the lung and quickly reaches all vascular endothelium.

The permeability increase caused by histamine is a modest one and can be reversed within several minutes by any H-1 receptor blocker.48 Whether histamine acts directly on the intercellular junction or via some action on the endothelial cells themselves is not known. Unfortunately, antihistamines probably do not affect the time course of the altered permeability edema occurring after Pseudomonas bacteremia in sheep (K. L. Brigham, personal communication).

Other possible specific chemical mediators of increased pulmonary microvascular permeability include the fibrinopeptides,50 salicylates,51 and complement activation.50,51

Physical Mechanisms

Stretched Pores. One possible mechanism that has received considerable attention is the “stretched pore” phenomenon.52,53 This implies that increasing transmural distending pressure widens the intercellular junctions.

According to the La Place equation, wall tension (T) is the product of distending pressure (P) and radius of curvature (r). The microvessels should be remarkably resistant to high distending pressures because of their small radius of curvature.54 Some examples are shown in Table 2. For comparative purposes, Burton was fond of pointing out that a piece of thin facial tissue (Kleenex) could withstand wall tensions of 50,000 dynes/cm before tearing. I do not know the tensile strength of endothelium

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Radius (cm)</th>
<th>Distending pressure (cm H2O)</th>
<th>Wall tension (dynes/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillaries</td>
<td>5 × 10^-4</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>Venules</td>
<td>50 × 10^-4</td>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>

TABLE 2 Wall Tension in Pulmonary Microvessels
but, even if it is only 1% that of Kleenex, it is sufficient to withstand pressures of 60 cm H2O in venules. If one views the alveolar wall capillary network (the largest surface area of the lung's microvasculature) as a sheet, then increasing the transmural distending pressure need not increase wall stress over the main portion of the sheet, but rather only at the "posts."55

The evidence for pore stretching in lungs is based mainly on electron microscopic studies with various tracers.53,54,55 I have discussed these reports previously and noted that the main problem appears to be the insensitivity of the methods. Schneeberger and Karnovsky56 have recently stated that distending pressures as high as 140 cm H2O during fixation have no discernible effect on the structure of endothelial junctions.

The physiological evidence, both clinical and experimental, is that the protein concentration in edema fluid and lymph is low in high pressure pulmonary edema, and this finding is generally incompatible with pore stretching.6 I do not mean to imply that such a phenomenon never occurs. Indeed, it probably occurs when there is increased hydrostatic pressure in microvessels with injured intercellular junctions as in permeability edemae.50 It also is likely that pore-stretching may occur at very high distending pressures.51 However, we must disabuse ourselves of the notion that pore-stretching occurs with every elevation of pressure. It clearly does not.

On the other hand, in high pressure edema, the lung fluids and lymph are blood-tinged. How is it possible that particles as large as red cells can appear in edema fluid without pores being stretched? One possibility is microvascular rupture with focal hemorrhages.56 Even at lower pressures, there is an increase in the number of red cells in edema fluid. These, I believe, can be accounted for by diapedesis.57 In altered permeability edema, by the way, an increased number of red cells is not characteristic of the lung fluid,16 even though the electron microscopic picture has been reported as one of severe microvascular endothelial disruption.58

Pressure and Velocity. A possible, indeed, a probable role exists for physical injury to microvascular endothelium as a common mechanism in several supposedly disparate forms of acute pulmonary edema. All of these seem to involve increased pulmonary vascular resistance proximal to the fluid exchange vessels, high altitude edema,18 neurogenic pulmonary edema,19 and the microembolism syndrome.20

We recently have begun to study the microembolism syndrome.21 Figure 1 shows the time course of lung lymph flow and its protein concentration following embolization with mineral oil. The rising resistance is accompanied by an increase in lung lymph flow (and lung water content is increased). The lymph-plasma protein ratio does not decrease. We also have raised pulmonary vascular resistance by selective lobar artery occlusion with balloons. Figure 2 shows results of one of these experiments.

The essential facts are as follows: (1) the increased fluid flux is accompanied by an increased protein flux as required by the definition of altered permeability edema; (2) the obstruction is non-uniform; although most of the lung's vascular bed is completely obstructed, a small portion remains patent receiving all of the cardiac output. Gibbon and Gibbon60 first described the phenomenon of edema following reduction of the pulmonary microvascular bed, produced by successive removal of lung mass. Visscher61 obtained similar results using emboli. Hultgren62 has also championed this theory, which he calls, "the pulmonary overperfusion syndrome." He found, by ligating successive lung lobes in anesthetized dogs, that he could cause pulmonary edema when he had obstructed approximately 80% of the lung's circulation. The edema fluid had a high protein concentration (H. N. Hultgren, personal communication).

Since high altitude pulmonary edema is no longer rare and because large proportion of patients with acute lung injury show microemboli, to understand how precapillary obstruction leads to altered permeability edema is of both theoretical and clinical significance. It cannot be simply a phenomenon of elevated microvascular pressure. We have elevated left atrial pressure to levels comparable to
the pulmonary artery pressures that we see following microembolism without producing this type of edema, that is, an edema fluid containing high protein concentrations. We speculate that some additional factor is involved. I believe this to be physical injury related to the increased linear velocity of blood flow. The restriction of the pulmonary vascular bed is so great that, for a given cardiac output, the velocity of flow through the microcirculation is three or more times more rapid than in the heaviest sustainable level of exercise. The kinds of injury I am suggesting may be due to the direct impact of blood against endothelium (inertial force) or to increased wall shear stress (frictional force) at places where there are rapid changes in the flow profile caused by the complex branching pattern of the microcirculation.

No one has demonstrated that pressure coupled with a high linear velocity of flow actually damages the lung’s endothelium. However, injurious effects of high linear flow velocities on systemic vascular endothelium have been reported. Saldeen agrees that high pressure is not the sole factor causing the altered permeability of the microembolism syndrome. He, however, favors chemical mediators, particularly fibrin degradation products.

### Treatment of Permeability Edema

In altered permeability edema it is important to start therapy aimed at preventing further damage and sustaining life. However, specific treatments that reverse the endothelial cell or intercellular junction derangement are not available.

Lacking these treatments, considerable attention has focused on ways to decrease the rate of edema fluid accumulation or to extract edema fluid from the lung. The concept is to manipulate the pressure terms in Equation 1. However, almost every manipulation in altered permeability edema is controversial. The clinical problem often includes more than altered microvascular permeability in the lung. Treatments benefitting pulmonary edema may not be helpful to the whole body. For example, Equation 1 predicts that, in altered permeability edema, any maneuver that decreases the pulmonary microvascular hydrostatic pressure (Pmv) will be beneficial. On the other hand, such decreases will affect cardiac output. Compromises must be made in order to preserve systemic oxygen delivery. The remainder of this review is a discussion of two of these controversial manipulations, namely, raising microvascular osmotic pressure (Pmv) by the infusion of different particles, and raising perimicrovascular hydrostatic pressure (Ppmv) by the use of positive airway pressure.

### Osmotic Agents

Osmotically active substances that may affect lung water are of two kinds: colloids (small molecules such as mannitol and urea) and macromolecules (plasma proteins or other colloids). In examining potential responses to changes in microvascular osmotic pressure (Pmv) by either class, one should remember that extravascular lung water is divided between intracellular and extracellular compartments in the ratio of about 2:1, that a change in osmotic pressure of 1 milliosmole (ΔΠ = 1 mOsm) is equivalent to a hydrostatic pressure change of 19 mm Hg, and that the normal plasma protein concentration of 6–7 g/dl is equivalent to about 1.5 mOsm.

### Crystalloids

Although electrolytes and sugars equilibrate with lung interstitial fluid within several minutes, Taylor and Gaar and Effros have shown that it is possible to extract some water from the lung in the first several seconds following sudden sustained increases or single bolus injections of osmotically active crystalloid agents in isolated, perfused lungs.

Effros maintains that the major portion of water he was able to extract came through endothelial cell membranes rather than through intracellular junctions because the extracted water contained very little solute. Since the endothelial cells, forming the lining of the microvascular bed in the lung, represent approximately 90% of the total extravascular tissue mass, it is likely that a substantial fraction of the extracted water came from within the endothelial cells themselves; that is, the endothelial cells were dehydrated.

The distinction between intracellular and extravascular water is important. Clearly, most of the excess lung liquid in edema is extracellular (in perivascular cuffs, interlobular connective tissue septae and, ultimately, in the alveolar space). The lung’s endothelial cell junctions are essentially freely permeable to crystalloids during filtration; their reflection coefficients are very low. Elevation of microvascular crystalloid osmotic pressure will not extract any significant amount of interstitial fluid and therefore would have little direct effect on the quantity of edema.

However, the extraction of water from cells that have swollen as a result of injury could be very important. Recently, Leaf reviewed the problem of cell injury and indicated that cell swelling is a common phenomenon. For example, Trunkey and associates showed that muscle cell swelling occurs in hemorrhagic shock. If the microvascular endothelium in the lung swells after injury, it may affect local blood flow such as has been demonstrated in brain, kidney, and heart. Powers (personal communication) has evidence that, following acute lung injury, hypertonic mannitol infusions improve lung blood flow distribution.

The dehydration of injured cells may indirectly affect the edema process itself if injured and swollen endothelial cells lose their ability to control intercellular junction integrity.

On the other hand, some investigators claim that crystalloid solutions are detrimental in experimental pulmonary edema.

### Macromolecules

It is claimed that concentrated protein solutions may be highly effective in the treatment of altered permeability edema. Other workers claim that macromolecular solutions are ineffective and possibly harmful in altered permeability edema.
When there is hypoproteinemia, a rise in microvascular protein osmotic pressures will improve the balance of forces across the microvascular endothelium, as predicted from Equation 1, provided the reabsorbed fluid volume is removed in some manner as is usually the case when diuretics are coupled with albumin therapy.

Even normally, however, the microvascular endothelium is not impermeable to proteins. Protein equilibrates in the lung's interstitial fluid more rapidly than it does with the body as a whole. A new steady state of plasma protein distribution is achieved within several hours.

When microvascular permeability to protein is increased, the equilibration of protein ought to proceed more rapidly. Indeed, Robin and associates showed the rapid appearance of tracer macromolecules in the airway fluid of two patients with "capillary leak syndrome." In sheep with increased permeability due to Pseudomonas bacteremia, we found accelerated equilibration of tracer protein between plasma and lung interstitium. Consequently, in altered permeability edema, the osmotic effectiveness of added macromolecules is reduced (decreased reflection coefficient in Equation 1), and whatever effect there is is of short duration.

Nevertheless, even in severely injured lungs, vascular integrity is not completely destroyed. In fact, it is likely that it is reasonably normal. Thus, for a certain time, even in the presence of altered protein permeability, an increase in plasma protein osmotic pressure ought to be effective in extracting some fluid from the lung. Quantitatively, what sort of increases in plasma protein osmotic pressure can be achieved? Let us suppose it is possible instantly to increase plasma protein (albumin) concentration from 6 g/dl to 12 g/dl. That is a huge increase and, in a 70-kg adult, would require an infusion of about 200 g of albumin (more than 800 ml of 25% solution). The plasma protein osmotic pressure would increase by approximately 65 mm Hg (3.5 mOsm). According to the manufacturer, this will extract approximately 2.8 liters of additional fluid (not just from the lung but from the entire body) into the circulation within 15 minutes. This is an overestimate, because it is based upon the dilution of plasma without considering the concentrating effect on total body extravascular water. Even if it were true, the lung should contribute only about 1% (28 ml), which is its proportion of total body water. If water extraction were increased, the equilibration of protein ought to proceed even more rapidly. Indeed, Robin and associates showed the rapid appearance of tracer macromolecules in the airway fluid of two patients with "capillary leak syndrome." In sheep with increased permeability due to Pseudomonas bacteremia, we found accelerated equilibration of tracer protein between plasma and lung interstitium. Consequently, in altered permeability edema, the osmotic effectiveness of added macromolecules is reduced (decreased reflection coefficient in Equation 1), and whatever effect there is is of short duration.

Marty suggested that albumin treatment is altered permeability edema would increase the concentration of protein in the extravascular interstitial fluid of the lung and thereby aggravate the edema. From Equation 1 it is clear that the source of energy for fluid filtration is the fact that microvascular hydrostatic pressure (Pmv), generated by the force of cardiac contraction, exceeds the perimicrovascular fluid hydrostatic pressure (Ppmv). The difference in protein osmotic pressure (Pmv − Ppmv) develops passively because the normal microvascular endothelium restricts protein flow relative to that of water. The actual magnitude of the protein osmotic pressure difference is dependent on the relative water to protein fluxes, namely, through the parameters K, α, and ω. Since microvascular hydrostatic pressure will never be less than perimicrovascular hydrostatic pressure, the protein concentration (osmotic) difference will never be reversed. At worst, if ω is very large and if α is zero, plasma and tissue protein osmotic pressures will be equal.

The loss of the osmotic negative feedback mechanism means that, for a given hydrostatic pressure, fluid filtration will be greater and, consequently, lymph flow and interstitial fluid content will be increased. However, with a freely permeable microvascular membrane, any added albumin will filter through the leaky membrane at the same concentration as it is in plasma (taking the worst possible example). Although there will be more protein in the edema fluid, it will not increase the volume of interstitial fluid or lung lymph flow. Albumin may not be very useful in altered permeability edema, but it is not bad in the osmotic sense.

Finally, let us consider the possibility that albumin has actions independent of any osmotic effect. Toung and coworkers found that large infusions of albumin completely blocked the formation of edema (weight gain) in isolated, perfused dogs lungs that had been damaged by aerosolized hydrochloric acid. Interestingly, the albumin load did not decrease lung weight, that is, did not osmotically extract any water. One interpretation of their results is that the albumin effect was manifest through a nonosmotic mechanism. Perhaps the hydrochloric acid and albumin interacted to form a coagulum which blocked the fluid leak sites.

**Positive Airway Pressure**

Clinical experience seems to support the use of positive airway pressure, particularly positive and expiratory pressure (PEEP), in the treatment of acute lung injuries from a variety of causes, all of which have increased vascular permeability as a common feature. Raising pressure within the thorax has many effects; my remarks are limited to the effects of PEEP on net fluid balance in the lung.

According to Equation 1, increasing the hydrostatic pressure external to the fluid exchange sites (Ppmv) ought to be beneficial, since it acts to oppose intravascular pressure. Indeed, for the very same reason that increased microvascular pressure is more serious in lungs with altered vascular endothelial integrity, so ought increases in Ppmv to be more beneficial. However, numerous investigators have found PEEP to decrease lung water content in edema. Some even claim it increases lung water content. How can the divergent results be reconciled? An important clarification in our understanding has been made by Be and associates. They showed in isolated, perfused rabbit lungs that increasing alveolar pressure, at constant vascular pressure, usually increases fluid filtration if lung volume is allowed to increase (as it does naturally when transpulmonary pressure increases). Under these conditions the lungs behave as if perimicrovascular hydrostatic pressure decreased. However, if lung volume is not allowed to increase (that is, pleural pressure is increased in parallel with alveolar pressure), the effect is always to decrease fluid filtration. This is equivalent to decreasing...
intravascular pressure at constant alveolar pressure, and is clearly predictable from Equation 1, but the former result is not predictable!

Be et al.\textsuperscript{96} explained their results by saying that positive alveolar pressure must be transmitted directly through the perimicrovascular interstitial fluid within the alveolar walls to the filtration sites where it, thereby decreases the sum of the pressures in Equation 1. When lung volume is allowed to increase, however, an additional factor comes into play. The fluid pressure in the loose connective tissue of the peribronchio-vascular spaces decreases relative to both alveolar and intravascular pressure. In this regard, it behaves as pleural pressure does.

Figure 3 is a two-compartment model that may be helpful in explaining their results. It shows the usual division of pulmonary vessels into alveolar and extra-alveolar ones, together with a similar division of the interstitial fluid compartment. The data of Be et al. can be interpreted in at least two ways. The simpler is that there are sites of fluid filtration in both regions. In the figure, this is represented by having a portion of the alveolar microvessels in the extraalveolar compartment. The alternative is that all the filtration sites are in the alveolar region, but changes in the bronchovascular connective tissue pressure (Pct) with lung volume permit it to act as a storage depot for filtered fluid.\textsuperscript{96} By draining away any alveolar wall filtrate, it acts to prevent a rise in tissue pressure there.

Unfortunately, these elegant experiments do not explain how PEEP affects lung fluid balance in intact experimental animals or in patients with pulmonary edema. Our own recent experiments in unanesthetized sheep\textsuperscript{96,97} have afforded us some additional insights. Both in normal sheep and in those with interstitial pulmonary edema due to increased microvascular hydrostatic pressure, we have found that 10 cm H\textsubscript{2}O PEEP does not significantly affect steady state lung lymph flow (Fig. 4).

In these experiments, the increased airway pressure caused an increase in lung volume as well as in pleural pressure and pulmonary vascular pressure. Cardiac output was not reduced by this level of PEEP. The protein osmotic pressures in plasma and lung lymph were not altered by the applied airway pressure.

Contrary reports on the effects of positive pressure ventilation by Drinker\textsuperscript{98} and by Baker\textsuperscript{99} dealt only with transients, not steady state conditions. In our sheep, there is a trend toward increased lung water content with PEEP, although the change is not statistically significant.

According to Equation 1, if fluid filtration was not affected, the applied airway pressure either was not transmitted to the fluid filtration sites or it was opposed by a counteracting force. Clearly, the pressure was transmitted because both left atrial and pulmonary artery pressures were elevated in every animal. The calculated value of microvascular pressure, shown in Figure 4, is due both to rises in left atrial pressure (increased pleural pressure) and to increased pulmonary artery pressure (compression of alveolar wall microvessels).

The synthesis of available data suggests that increasing alveolar pressure does, indeed, increase perimicrovascular fluid pressure, but this is opposed by a similar rise in microvascular pressure. The fact that lung volume increases with PEEP means that extraalveolar connective tissue pressure decreases relative to alveolar and microvascular pressures and thereby increases the pressure gradient draining alveolar wall fluid into the connective tissue sumps (bronchovascular cuffs).

### Alveolar Membrane

Although this Review is supposedly limited to changes in microvascular permeability, it is clear that the alveolar epithelium is an additional barrier to fluid exchange and ought to be considered briefly. Normally, epithelial barriers have much lower permeability to solutes than do endothelial barriers. The lung is no exception. Both physiologically\textsuperscript{62,100} and by ultrastructural analysis,\textsuperscript{53,56} the alveolar epithelium is a severe barrier not only to mac-

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**Figure 3** Lung pressures relevant to fluid filtration and storage. When lung volume increases, the pressures in the extra-alveolar compartment (pleural, Ppl, and interstitial connective tissue, Pct) decrease relative to the pressures in the alveolar compartment. In the alveolar compartment the pressures (alveolar, Palv; microvascular, Pmv, and perimicrovascular, Ppmv) all rise. Pulmonary arterial pressure, Ppa, generally increases relative to Ppl, whereas pulmonary venous pressures, Ppv, reflects the change in Ppl. In terms of lung fluid, filtration is not much affected but storage in the extraalveolar connective tissue space is slightly increased.

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**Figure 4** Tissue course of the effect of 10 cm H\textsubscript{2}O continuous positive airway pressure breathing (CPAPB) in an unanesthetized sheep.
The alveolar epithelium delays the onset of alveolar flooding in pulmonary edema, as if it were freely permeable to plasma proteins. Indeed, the available evidence indicates that, in all forms of edema, the alveolar membrane behaves as if it were freely permeable to plasma proteins. There is no distinction as far as the alveolar epithelium is concerned between high pressure and altered permeability edema.

Although the phenomenon is well-documented, the mechanism by which tight epithelial junctions suddenly give way and permit free access of interstitial edema fluid and protein to the alveolar space in contoversial. No one has actually seen the pathway by which the fluid flows.

Macklin long ago suggested that there were specialized areas in the terminal airways for the passage of fluid, cells, and particulate material between the lung's interstitium and air spaces. Gee and Staub have evidence that the transport of proteins from air spaces into lung tissue is not explainable by a simple mechanism such as diffusion through alveolar epithelial pores. Egan, on the other hand, believes that stretching of the alveolar epithelium, as well as increases in lung volume, may act to open intracellular junctions. The problem with that explanation for pulmonary edema is that the alveolar epithelium is not stretched. Indeed, the volume of the alveoli decreases as they fill with fluid.

Although it seems reasonable that an intact alveolar epithelium delays the onset of alveolar flooding in pulmonary edema, we actually have no proof of such a function. My opinion is that the site of injury leading to disastrous consequences in increased permeability edema is the microvascular endothelium, not the alveolar epithelium.

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