Capillary Leak Syndrome With Pulmonary Edema

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In two patients with a diffuse abnormality of capillary permeability possibly related to circulating endotoxin, loss of plasma into the tissues (capillary leak syndrome) produced hypovolemic shock, generalized edema, hemoconcentration, and florid pulmonary edema. Pulmonary edema fluid (PEF) was collected and its chemical composition compared to plasma. A number of solutes including the various plasma proteins were in near chemical equilibrium between plasma and PEF. Intravenous administration of dextran 70 (molecular weight 70,000) and dextran (molecular weight 500,000) (in one patient), led to accumulation of these compounds in PEF at a rate consistent with abnormally high pulmonary capillary permeability. These cases document the development of pulmonary edema secondary to increased pulmonary capillary permeability. Possibly, a number of pulmonary diseases (collectively called adult respiratory distress syndrome) result from increased pulmonary capillary permeability, increased alveolar epithelial permeability, or abnormalities of pulmonary interstitial solute removal.

The role of increased capillary permeability in the pathogenesis of pulmonary edema has often been emphasized on a theoretical basis. There has been, however, little documentation of such a mechanism in clinical circumstances. In experimental animals, pulmonary edema related to increased permeability has been produced by administration of α-naphthylthiourea[1] and alloxan.[2]

We report two cases in which a general alteration of capillary permeability was present. This led to a loss of plasma into the tissue, producing shock, generalized peripheral edema, and pulmonary edema. In each patient, the degree of pulmonary edema was so extreme that pulmonary edema fluid (PEF) could be collected in sufficient amounts to be analyzed chemically. The course of the illness in each patient is described. We discuss the implications derived from these patients for an understanding of transpulmonary water and solute exchange under conditions of increased capillary permeability and emphasize the possible relationship between increased pulmonary capillary permeability and a variety of disorders.

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Patient Summaries

PATIENT 1.—A 24-year-old woman, gravida 1, para 0, abortion 0, was admitted in active labor. The pregnancy had been uneventful with no evidence of toxemia. Findings of physical examination and laboratory studies were normal. After 16 hours of labor, a healthy boy was delivered. The midline episiotomy extended by a tear into the rectum and required surgical repair. Following an uneventful 24 hours, temperature rose to 38.9 C (102 F) with chills and perineal pain. There was costovertebral angle tenderness, left labial swelling, induration, and erythema with extension into the left buttock.

The following day (day 4) *Klebsiella* (10^7 colonies per milliliter) was cultured from the urine and *Bacteroides funduliformis* from the vagina. Fever persisted and treatment with aqueous penicillin G potassium, 20 million units administered intravenously every eight hours, and kanamycin sulfate, 500 mg administered intramuscularly every two hours, was begun without improvement. On the fifth day, fluids were administered intravenously because of poor oral intake and vomiting. The white blood cell count (WBC) was 59,000/cu mm with a shift to the left. Blood pressure was 100/90 mm Hg; pulse rate, 120 beats per minute and regular; and respirations, 25/min.

On day 6 blood pressure was 80/60 mm Hg; pulse rate, 130 beats per minute; and central venous pressure (CVP), 3 cm H_2O. Five hundred milliliters of 0.9% sodium chloride administered intravenously improved blood pressure and urinary output which had fallen to 35 to 45 ml/hr. Twitching and irritability were treated with phenobarbital and calcium gluconate. White blood cell count was 64,000/cu mm; hematocrit reading, 57%, level of blood urea nitrogen (BUN), 31 mg/100 ml; and level of magnesium, 1.4 mEq/liter. Urinalysis showed specific gravity, 1.027; pH, 6.5; and protein, 4+, loaded with WBC and coarse and fine granular casts.

On day 7, the patient was anuric and in shock with blood pressure 30/0 mm Hg; CVP, 0 cm H_2O; and pulse rate, 150 beats per minute. One thousand milliliters of 5% normal human serum albumin and 3,350 ml of 5% dextrose in saline were given; blood pressure rose to 110/60 mm Hg, and CVP to 16 cm H_2O. Urine volume was 2,045 ml for the next 24 hours. The patient became more alert but had two seizures requiring diazepam and phenobarbital.

Over the next two days, respiratory distress was noted with a respiratory rate of 40/min and basilar rales. Digoxin and intermittent positive pressure breathing (IPPB) with isoproterenol were administered, along with oxygen given nasally. Five hundred milliliters of 5% normal human serum albumin with 2,600 ml of 5% dextrose in saline resulted in urine output of 1,500 ml. Tetracycline hydrochloride, 100 mg, was administered intramuscularly ev-

ery eight hours. The following day, there were increasing rales, falling urine output, and increasing pulmonary infiltrates. Blood pressure was 140/90 mm Hg; pulse rate, 150 beats per minute; CVP, 10 cm H_2O; respirations, 16/min; and temperature 38.9 C. The sensorium was depressed, and there was scleral edema and dullness in the right inferior hemithorax with bilateral rales. The abdomen was distended and dull to percussion. There was pitting edema from ankles to lower abdomen. A grand mal seizure necessitated tracheal intubation, and ventilatory support with 40% oxygen resulted in arterial oxygen pressure (Pao_2) of 97 torr, and arterial carbon dioxide pressure ($Paco_2$), 27 torr. Chest x-ray film showed confluent consolidation in both mid-lung fields and bilateral pleural effusions. Laboratory data at this time included a hematocrit reading of 51% and a blood volume (determined with iodinated I 131 serum albumin) of 1.6 (normal 3.4) liters. Pulmonary infiltrates increased, Pao_2 fell, and concentration of inspired oxygen (Fio_2) was increased to 40% to 50% with assisted ventilation.

On the 12th day, the patient's condition worsened and fulminant pulmonary edema was present without clinical evidence of left ventricular failure and with a CVP of 8 cm H_2O. Three to five milliliters of PEF per minute could be collected from the ventilator connecting tubing. Hemodialysis was performed to treat overhydration. Several episodes of cardiac arrest were successfully treated. Arterial oxygen pressure fell to 30 torr with Fio_2 of 100% using IPPB, and the patient was placed on continuous positive pressure breathing (CPPB) (15 cm H_2O) which raised Pao_2 to 130 torr transiently. (Intermittent positive pressure breathing refers to the use of a respirator which produces air flow by means of intermittent delivery of positive pressure. At some phase of expiration intrathoracic pressure is atmospheric. Continuous positive pressure breathing also produces air flow by the intermittent delivery of positive pressure. Intrathoracic pressure, however, is consistently maintained above atmospheric pressure.) Because of the perilous condition, 60 gm of high molecular weight dextran (mol wt 500,000), were given intravenously over an eight-hour period. With this treatment the outpouring of PEF ceased. The next morning the patient's sensorium had cleared dramatically, peripheral edema was less, and the chest x-ray film showed improvement. Tracheostomy was performed and ventilatory support continued with CPPB of 10 to 15 cm H_2O.

Over the next seven days, the sensorium remained stable. The patient responded to simple commands and was able to take liquids orally. Renal function gradually improved and BUN level fell. There was a weight loss of 8 kg in ten days. Several attempts to change from controlled to assisted ventilation were unsuccessful. Satisfactory Pao_2 (over 50 torr) could be maintained with Fio_2 of 40% to 60%; the CPPB, however, could not be reduced. Several episodes of subcutaneous and mediastinal emphysema and one life-threatening episode of endotracheal hemorrhage occurred.

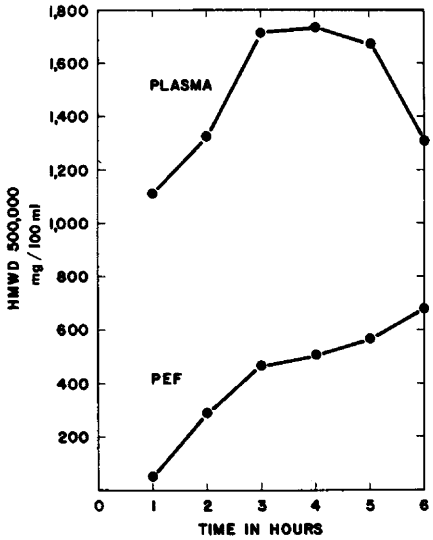
There was gradual improvement during the next week, but chest x-ray film showed persistent bilateral consolidation. The chest findings were quite sensitive to fluid replacement, and volumes of as little as 600 ml excess or deficit were reflected by changes in roentgenographic findings and Pao_2.

On the 26th postpartum day, there was a second tracheal hemorrhage requiring 500 ml of whole blood. Level of BUN had fallen to 47 mg/100 ml and urinary output approached 2,000 ml/day without diuretics. Electrolytes were normal and serum protein rose to 5.5 gm/100 ml. Over the next five days, all attempts at decreasing ventilatory support were unsuccessful. Attempts to decrease peak pressure, tidal volume, or rate resulted in rapid increases of $Paco_2$ and decreases of Pao_2. Bilateral pneumothoraces occurred and chest tubes were inserted. In desperation, extracorporeal oxygenation with a membrane lung was carried out for 18 hours. The pupils became bilaterally dilated and the use of the membrane oxygenator was discontinued. The patient died 24 hours later on the 34th postpartum day.

Postmortem examination revealed far advanced interstitial pulmonary fibrosis. There were numerous intra-alveolar hyaline membranes. In addition, there was rupture of the lower lobe of the right lung presumably related to the use of CPPB. The left ventricle was not remarkable.

PATIENT 2.—A 62-year-old woman had a two-day history of watery nonbloody diarrhea. During the previous ten days she had a low grade fever, anorexia, malaise, myalgia and arthralgia, and a 5-kg weight loss. Ulcerative colitis had been diagnosed 15 years earlier.

On admission, blood pressure was 110/70 mm Hg; pulse rate, 108 beats per minute and regular; respirations, 20/min; and temperature, 36.7 C (98 F). Abnormal findings of the physical examination were limited to the abdomen and included distention, tympany, high-pitched bowel sounds, and left lower quadrant (LLQ) tenderness without evidence of peritoneal irritation.



Dextran (mol wt, 500,000) time-concentration curves in plasma, and PEF in patient 2. HMWD signifies high molecular weight dextran.

White blood cell count was 6,500/cu mm with mild left shift; urine was normal. Other values were as follows: hematocrit, 32%; BUN, 13 mg/100 ml; Na, 134 mEq/liter; K, 3.8 mEq/liter; Cl, 94 mEq/liter; HCO_3, 27 mEq/liter; Ca, 7.8 mEq/liter; total protein and fractions were normal. Chest x-ray film was unremarkable and heart size was normal. Abdominal x-ray films were compatible with toxic megacolon. Electrocardiogram showed nonspecific ST-T segment changes. Low-salt, low-roughage diet, and prednisone therapy, 20 mg/day, were started. Over the next three weeks, the patient's course was unchanged. After one month, because of persistent toxic reaction, colonic distention, and anorexia, total colectomy and ileostomy were performed. Two areas of colonic perforation were found and considerable fecal contamination of the peritoneal cavity occurred. Toward the end of the operation, extensive bleeding from all areas of dissection was noted.

Thirty-five hundred milliliters of whole blood, 2,000 ml of balanced electrolyte solution, and 500 ml of 5% normal human serum albumin were given during the surgery. Systolic blood pressure remained at 70 to 90 torr. In the recovery room, bleeding continued and averaged 200 ml/hr from the perineum alone.

Thrombocytopenia, slight hypofibrinogenemia, and normal levels of factors VIII and XIII confirmed consumption coagulopathy, and heparin sodium, 10,000 units, was given intravenously. Over the next 15 hours, 7,500 ml of whole blood along with platelet transfusions were required. Systolic blood pressure remained 70

Composition of Plasma and Pulmonary Edema Fluid				
	Patient 1		Patient 2	
	Plasma	PEF	Plasma	PEF
Na^+, mEq/liter	148	168	137	141
K^+, mEq/liter	4.1	4.2	4.0	4.2
Cl^-, mEq/liter	95	113	93	97
Glucose, mg/100 ml	133	86	123	114
Total protein, gm/100 ml	5.0	4.0	3.1	2.9
Albumin, gm/100 ml	3.1	2.6	2.1	2.0
α_1 globulin, gm/100 ml	0.3	0.3	0.2	0.2
α_2 globulin, gm/100 ml	0.4	0.2	0.2	0.2
β = globulin, gm/100 ml	0.5	0.4	0.2	0.3
γ = globulin, gm/100 ml	0.7	0.5	0.4	0.2
Dextran 70, mg/100 ml	1,000*	527	611	545
Fibrinogen, mg/100 ml			48	54
Dextran (mol wt 500,000), mg/100 ml†			1,309	680

* Plasma analysis lost; value calculated from distribution of dextran through extracellular volume.

† Six hours after infusion of dextran (mol wt 500,000) started.

to 90 mm Hg with urinary output decreasing from 50 to 25 ml/hr.

There was postoperative bleeding and blood pressure fell to 40/0 mm Hg and urine output to 5 ml/hr. Rapid infusion of mannitol, lactated Ringer's solution, and dextran 70 raised urinary output transiently to 40 ml/hr. Because of respiratory distress, tracheostomy was performed and ventilatory assistance begun.

During the next 24 hours, peripheral edema developed with ascites, and severe pulmonary edema developed without evidence of left ventricular failure. Plasma-like liquid poured out of the endotracheal tube at a rate of 2 ml per minute. With controlled ventilation on 100% oxygen and CPPB of 10 to 20 cm H_2O, Pao_2 was 40 torr; $Paco_2$, 48 torr; and pH, 7.32. One thousand milliliters of 10% dextran (mol wt 500,000) was given over several hours. However, shock and pulmonary edema persisted and the patient died on the third postoperative day.

Postmortem examination showed acute pulmonary edema and red hepatization. There were numerous intra-alveolary hyaline membranes. The left ventricle appeared normal. There was generalized peritonitis.

Methods

Pulmonary edema fluid was collected from the expiratory tube of the respirator, timed samples being obtained so that volume flow could be estimated. Blood samples were obtained at approximately the midperiod of each PEF sample collection. Concentrations of Na^+ and K^+ were determined by flame photometry; Cl^- by electrometric titration.[3] Glucose was measured enzymatically using glucose oxidase. Total protein concentrations on PEF and plasma were determined by the Lowry technique.[4] The quantitation of proteins into separate fractions was accomplished by cellulose acetate electrophoresis. Fibrinogen was determined turbidometrically.[5] Dextran analysis was performed by the anthrone method.[6] In patient one, PEF was obtained one hour after the administration of dextran 70 (mol wt 70,000). In patient 2, 100 gm of dextran (mol wt 500,000) was administered intravenously as a 10% weight in volume (w/v) solution over six hours and sequential samples of plasma and PEF analyzed. This patient had received dextran 70 approximately 24 hours prior to the infusion of dextran (mol wt 500,000) and the concentration of this solute was subtracted from total dextran concentration to obtain the concentration of dextran (mol wt 500,000) in plasma and PEF. Chest x-ray films to determine the effect of diuresis and of CPPB were obtained using the same focal length and the same kilowattage and amperage on each film for purpose of comparison. Blood gas determinations and blood volume (iodinated I 131 serum albumin technique) measurements were performed as dictated by the clinical status of the patients.

Results

Chest x-ray films showed diffuse intra-alveolar and interstitial involvement with marked clearing after diuresis of as little as 600 ml. The values for the various chemical species in plasma and PEF are listed in the Table. Glucose, Na^+, K^+, and Cl^- appeared to be in equilibrium in both fluids although the electrolyte concentrations in PEF were slightly higher than those in plasma. Protein concentrations in PEF of both patients were lower than those in plasma, but albumin (mol wt approximately 60,000), globulins (mol wt approximately 150,000), and fibrinogen (mol wt 340,000) were present in PEF. One hour after the infusion of dextran 70 in patient 1, this compound was present in PEF in a concentration that was approximately 50% of its concentration in plasma. In patient 2, two hours after infusion of dextran 70, this solute was present in PEF in a concentration that was approximately equal to that of plasma. Following the infusion of dextran (mol wt 500,000) there was a sequential rise in dextran concentration in both plasma and PEF and by six hours the value in PEF approximated 52% of that in plasma (Figure). Red blood cells (RBC) were present in all samples of PEF. The hematocrit reading of all samples was less than 1%. The low hematocrit reading and the progressive orderly rise in PEF dextran levels strongly suggest that the mechanism of pulmonary edema is not simple alveolar hemorrhage (pulmonary epistaxis). If this were true, PEF would have a higher hematocrit value and the time concentration curve for dextran would be more erratic. Moreover, the concentration differences for a number of solutes indicate that the PEF resembles but is not identical to plasma. In some areas, however, there might have been sufficient disruption of exchange sites so that RBC find their way into alveolar spaces.

Comment

Both patients exhibited abnormalities of capillary permeability involving many vascular beds as shown by massive subcutaneous edema, fluid accumulation in serous cavities, hemoconcentration (patient 1), and hypovolemic shock. In neither pateint was a cause for the capillary dysfunction identified and capillaries appeared histologically normal at postmortem examination.

The development of pulmonary edema related to increased pulmonary capillary permeability appears

to be a tenable hypothesis. Plasma leakage in many capillary beds suggested that this might likewise be taking place in the lung. In patient 1, the intravenous administration of dextran 70 led, in one hour, to a concentration in pulmonary edema fluid approximately 50% of that found in plasma. This represents more rapid passage of this molecule than we have noted in studies of pulmonary capillary permeability in dogs (Robin and Gaudio, unpublished data). In patient 2, the rapid passage of high molecular weight dextran (mol wt 500,000) from the vascular bed into PEF is strong evidence for increased pulmonary capillary permeability.

Exclusion of cardiogenic pulmonary edema as a primary mechanism is of obvious importance. Pulmonary "capillary" left atrial or left ventricular end diastolic pressures were not measured. Thus, the possibility of cardiogenic pulmonary edema cannot be absolutely excluded. Neither patient, however, had evidence of sufficiently severe left ventricular dysfunction to explain the development of pulmonary edema which was present without substantial elevation of central venous pressure. Furthermore, postmortem examination did not reveal evidence of left ventricular disease. In this respect we have recently reviewed data on a patient who closely resembles patient 1. This patient was a 32-year-old, gravida 3 housewife admitted in labor to the obstetrical service of the University of Washington Hospital in Seattle. Following cesarean section the patient developed fulminant pulmonary edema with the production of large volumes of frothy PEF resembling plasma. Central venous pressures were not abnormally high and there was no evidence of primary left ventricular disease. Cardiac catheterization revealed a mean pulmonary artery pressure of 35 mm Hg and a pulmonary wedge pressure of 15 mm Hg. Although these pressures are moderately elevated, it is clear that the massive pulmonary edema could not be explained on the slight elevation of pulmonary "capillary" pressure. The reports of Riordan and Walters[7] and of MacLean et al[8] show that pulmonary edema does occur in endotoxin shock despite normal pulmonary capillary pressure. These considerations strongly suggest that the pulmonary edema in our two patients was related to alterations of pulmonary capillary permeability.

The intravenous administration of 60 gm of high molecular weight dextran (mol wt 500,000) in patient 1 was associated with dramatic improvement. Dextran administration was undertaken to provide an osmotically active material which did not rapidly escape from capillary beds. Improvement occurred after only 20% of the planned dose (300 gm) was administered. The amount was osmotically insignificant. It is certainly possible that the sudden improvement was not causally related to dextran administration. On the other hand, the temporal association between its administration and improvement was impressive. Ten percent solutions of dextran, (mol wt 500,000) are extremely viscid and, conceivably, the material acted to seal capillaries mechanically. In patient 2, administration of 100 gm of dextran (mol wt 500,000) was not effective and this solute rapidly leaked through the pulmonary capillaries to appear in PEF. It is possible that the degree of capillary injury was more severe in patient 2. Our overall impression is that this substance would be worth additional trial in other patients with diffuse capillary leak. We would, therefore, appreciate hearing from physicians with such patients.

The pathogenesis of the capillary leak seen in our patients is not entirely clear. In patient 1, it is possible that the capillary abnormality resulted from circulating endotoxin related to postpartum infection. This possibility seems even more likely in patient 2, since capillary leakage closely followed peritoneal soiling caused by multiple perforations of the colon.

A number of studies have emphasized the occurrence of vascular damage to capillaries and small blood vessels in septic shock or following endotoxin administration.[9-11] Chien et al[12] specifically studied the effect of endotoxin on capillary permeability. They demonstrated that endotoxin produces marked increases in capillary permeability to macromolecules. Following the intravenous injection of *Escherichia coli* endotoxin, lymph flow from the thoracic duct and lymph concentrations of macromolecules (albumin and dextran mol wt 250,000) increased. These findings suggested increased capillary permeability. Snell and Ramsey reported development of pulmonary edema following the intravenous administration of endotoxin in dogs.[13] Riordan and Walters reported seven patients with bacterial shock and pulmonary edema. In these patients, left ventricular disease and overhydration were specifically excluded.[7] MacLean et al reported a patient with septicemia and pulmonary edema with a normal pulmonary wedge pressure and normal serum albumin concentration.[9]

Infection, however, may not be the only pathogenic factor in the capillary leak in our patients. Two patients described in the literature closely resemble our first patient. Clarkson and co-workers reported an otherwise normal young woman who, on repeated occasions, had sudden and marked leakage of plasma from the vascular bed[14] which was associated with hypovolemic shock, hemoconcentration, and generalized edema, apparently related to intermittent alterations of capillary permeability. The episodes of plasma loss had a consistent relationship to menstrual periods. During one episode, she died. It seemed improbable that her disorder could be related to recurrent infection.

A second case, reported by Luke and Rubenstein,[15] was that of a 28-year-old postpartum woman who completed her second pregnancy at full term and delivered a healthy boy after 18 hours of labor. On the third postpartum day edema of the vulva, perineum, buttocks, and thighs followed by shock, hemoconcentration, and generalized edema developed. During a 48-hour period the patient received 14 liters of plasma and 238 gm of albumin in addition to other fluids. She died on the fifth postpartum day. At postmortem there was generalized edema, both pleural

cavities were filled with fluid, and there was pericardial effusion as well as ascites. Although no etiological basis was established, it was considered unlikely that the disorder was related to infection.

Probably a variety of etiological factors can lead to a diffuse increase in capillary permeability with subsequent loss of plasma into tissues. Infection is one important cause. The pregnant or menstruating patient may be at special risk because of hormonally induced vascular alterations. The relative sparseness of reports of the capillary leak syndrome may be related to lack of recognition.

Since the decisive factor with respect to survival in our patients was fulminant pulmonary edema, it is useful to discuss the permeability of distal pulmonary exchange sites. Structurally these exchange sites include two cell types: endothelial cells comprising pulmonary capillaries, and the elongated cytoplasmic extensions of alveolar epithelial cells forming alveolar walls. Junctions between these cells share a common basement membrane for a considerable extent of their length but ultimately diverge to form the interstitial space.[16]

There is general agreement that the permeability of the pulmonary capillary endothelium does not differ greatly from that of other capillaries. There is a relatively high permeability to water and solutes such as small ions (Na^+, K^+, Cl^-), uncharged metabolites such as urea and glucose, and even relatively high molecular weight compounds including proteins.[17]

The permeability of alveolar epithelial cells is less well defined. Studies based on relatively short time periods suggest that it is low. Chinard,[18] using an ingenious indicator dilution technique, concluded that the permeability properties of the alveolar-pulmonary capillary junction constituted an effective barrier to even low molecular weight, highly lipid soluble substances like urea. These studies, however, involved a single passage through the pulmonary circulation (less than one second) and fundamentally concerned liquid-to-air transport. Having studied the permeability of isolated saline-filled perfused rabbit lung to Na^+, urea, glucose, and sucrose, Wangensteen et al[19] found that the overall barrier was quite resistant to the passage of small lipid-insoluble solutes, but that permeability characteristics of the pulmonary capillary wall were similar to those of heart and skeletal muscle. They concluded that the main resistance to transport across the barrier was the alveolar epithelium and that solutes found in alveolar liquid may pass across the alveolar epithelium by means of small, relatively unselective leaks. Taylor and Garr[20] used a technique involving osmotic transients and calculated a pore radius of 6 to 10 Angstroms for the alveolar membrane and one of 40 to 50 A for the pulmonary capillary membrane. They concluded that the alveolar membrane represents a tight cellular-type structure, whereas the pulmonary capillary membrane represents a highly permeable porous structure.

Using histochemical techniques, Schneeberger-Keely and Karnovsky studied alveolar-membrane permeability to a protein, horse-radish peroxidase. Ninety seconds after injection, horse-radish peroxidase had passed through endothelial junctions into underlying basement membranes. Horse-radish peroxidase was demonstrated in pinocytotic vesicles of both endothelial and epithelial cells, but the role of these vesicles in net protein transport appeared to be minimal.[21]

There are, however, observations which do not fit with the concept of a tight cellular-type membrane structure for the alveolar epithelium.

Kylstra,[22] utilizing somewhat longer periods of observations, studied pulmonary lavage as a potential substitute for hemodialysis. Following instillation of saline within alveoli many solutes present in plasma appeared in alveolar liquid. Clinically, it is well known that a plasma-like liquid may be lost from the lung during pulmonary edema, suggesting that, under these circumstances, a wide variety of solutes can cross the alveolar epithelium. A wide variety of pharmacologic agents are absorbed into the vascular compartment following aerosol administration. Although the precise location of absorptive sites is not known, it is reasonable to assume that some absorption occurs at an alveolar level.[23]

Our laboratory has studied the movement of various solutes across alveolar pulmonary capillary-alveolar epithelial junctions in the saline-filled lung of the dog. These solutes included sucrose, inulin, and dextrans of various molecular weights, molecules which are not able to cross the cell membranes of most cells. The studies differed from most studies of transalveolar solute transport in that periods involving hours and not minutes were utilized. It was shown that, in the presence of liquid-filled alveoli and given sufficient time, these solutes cross pulmonary distal exchange sites bidirectionally. Thus, from the standpoint of overall permeability properties these exchange sites are considerably more permeable than most cell boundaries (Robin and Gaudio, unpublished data).

It should be emphasized that our studies do not define the exact pathway by which the solutes pass between alveolar spaces and pulmonary capillaries. It is possible that transport does not occur directly across cellular basement membranes but across unselective sites. It is also possible that the solute transport occurs by pinocytosis. The transpulmonary passage of a variety of solutes, however, would appear to be of clinical importance regardless of the precise pathway and mode of transport.

The ready penetration of water and solutes including proteins of normal pulmonary capillary endothelial cells suggests that disposal mechanisms for handling overflow are of critical importance. Small pulmonary lymphatics are a major site of liquid and solute disposal. In particular, the lymphatics play a key role in protein removal from the interstitial space. This not only protects the integrity of the interstitial space, but also provides a mechanism for ultimately returning the plasma proteins to the circulating blood volume. In most tissues, accumulation of water and solutes would not profoundly affect function. In the interstitial space of

the lung, however, such accumulation leads to disordered pulmonary mechanics and gas exchange.

Even in patients with normal pulmonary capillaries, the administration of plasma expanders (mannitol, albumin, dextran) may lead to interstitial accumulations. In the face of increased permeability of the pulmonary capillaries, the accumulation of water and solutes may be accentuated.

Interstitial accumulations, if sufficiently prolonged, may lead to transalveolar transport and intra-alveolar accumulation of even macromolecular solutes. Thus, given an abnormally high pulmonary capillary permeability (as hypothesized in our two patients) the development of fulminant intra-alveolar pulmonary edema is not surprising. In addition to increased pulmonary capillary permeability, increased alveolar epithelial permeability or abnormalities of pulmonary interstitial disposal mechanisms may also lead to pulmonary edema.

Alterations of pulmonary capillary or alveolar epithelial permeability may be the underlying mechanism in a diverse group of disorders whose pathogenesis is obscure, eg, shock lung, respirator lung, uremic lung.

In recent years, an attempt has been made to collect a number of these conditions in a common group designated as adult respiratory distress syndrome.[24,25] Major emphasis has been placed on the development of impaired gas exchange and other pulmonary lesions in shock, following pulmonary or generalized trauma, after prolonged exposure to high oxygen concentration, and prolonged respirator treatment with intermittent positive pressure with or without CPPB. Other possible etiological factors include cardiac pulmonary edema, atelectasis, aspiration, bacterial or viral infection, pulmonary contusion, alveolar hypoxia or hyperoxia, and pulmonary hypoperfusion (embolism, vasospasm, intravascular clotting). The mortality in these patients is high. At autopsy, the lungs appear heavy and liver-like. Patients in early stages show interstitial edema and hyaline membrane, while those patients who have survived longer demonstrate more completely destroyed pulmonary parenchyma with alveolar wall necrosis and interstitial fibrosis. The similarity of adult respiratory distress syndrome to the picture seen in our two patients is striking.

We can speculate that the common denominator may be an alteration of pulmonary capillary or alveolar epithelial permeability or both. As a result, a variety of solutes found in plasma, including proteins, ultimately leak into the intra-alveolar spaces. With denaturation of the proteins and conversion of fibrinogen into fibrin, a common histologic appearance results.

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