SPECIAL ARTICLE

Pulmonary Edema
The Water-Exchanging Function of the Lung

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SUMMARY
The pathogenesis of clinical pulmonary edema is considered in the light of recent physiologic and anatomic insights. Pulmonary edema is depicted as a persistent imbalance between the forces that move water into the extravascular spaces and the biologic devices for its removal. In the normal lung, intricate anatomic arrangements coupled with elaborate physiologic mechanisms maintain the gas-exchanging surfaces moist and free of excess protein. A transient excess of water in the interstitial space is associated with an increase in lymphatic flow. Should the excess rate of formation persist or increase, pulmonary edema may become manifest clinically, first as interstitial edema and then as alveolar and airway edema. The distribution of edema within the lung may be nonuniform, often favoring the central portions early in its genesis but later redistributing under the influence of gravity. A critical limitation in anatomic design is imposed by the narrow channels through which lymph passes out of the thorax into systemic veins. Accordingly, the pulmonary lymphatic system, which seems better suited to return proteins than water to the systemic circulation, may become a limiting factor in relieving pulmonary edema in states of unremitting water movement into the extravascular spaces.

The anatomic and physiologic principles are then applied to current clinical enigmas, such as "shock lung," high-altitude pulmonary edema, and the edema that follows an overdose of narcotic agents, such as heroin. In "shock lung" after severe systemic hypotension, nonuniform pulmonary hypoperfusion is identified as the critical pathogenetic factor in the pulmonary edema that occurs during recovery, i.e. after systemic blood pressures have been restored to normal by large transfusions. The corresponding etiologic role for high-altitude pulmonary edema is attributed to anatomic variations in precapillary resistances in the lungs during a burst of severe pulmonary hypertension. The situation is more complicated for the pulmonary edema that follows narcotic overdosage since not only may the medication elicit severe respiratory depression, arterial hypoxemia, respiratory acidosis, and their sequelae—left ventricular failure, leakage of minute pulmonary vessels, and impaired lymphatic drainage—but the self-administered medication may be contaminated with substances that may, per se, cause minute pulmonary vessels to leak.

In the lungs, as in the gills, gas exchange occurs across thin moist membranes. For these membranes to operate effectively, they must be kept free of flooding. The fundamental mechanism by which undue accumulation of water is avoided is a precise

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balance of hydrostatic and osmotic forces across capillary walls that behave physiologically as though they are impermeable to protein. Nevertheless, some water (and protein) does escape from the capillary into the alveolar septum. To cope with these leaks, which would ultimately derange gas exchange, the lung is bailed out by an elaborate system of lymphatics that returns to the systemic veins the extract of plasma that is left behind in the pulmonary interstitial space by blood streaming through the pulmonary capillaries.

Subsidiary devices, to be considered subsequently, complete the apparatus for maintaining the alveolar-capillary surfaces moist but unflooded. The net effect of these contrivances is that the quantities of extravascular water and proteins in the normal lung remain quite stable from day to day, even though they may fluctuate transiently in the course of daily activities. In disorders, such as heart failure or emphysema, the levels are reset. However, variations in lung water are usually too subtle to detect until the extravascular water space has doubled or tripled. Consequently, clinical criteria for pulmonary edema are more apt to identify waterlogging of the lungs than an early stage of water excess.

Ever since Welch showed experimentally that acute left ventricular failure caused flooding of the lungs, cardiologists have accepted increased hydrostatic pressures as the most important cause of clinical pulmonary edema. Subsequently, others identified a second major category in which alveolar-capillary barriers became extraordinarily porous because of injury by toxic inhalants. Since then, clinicians have found it expedient to distinguish between "hemodynamic" and "permeability" types of pulmonary edema.

In recent years, attention has focused on novel varieties of pulmonary edema that are not readily sorted into either of these two categories. Among these are the high-altitude pulmonary edema, "shock lung," and the pulmonary edema that complicates overdosage of heroin. The failure of traditional concepts to account for these dramatic forms of pulmonary edema has not only stimulated research into their pathogenetic mechanisms but has also prompted reexamination of conventional notions about water exchange and accumulation in the lungs.

The present essay takes advantage of recent insights into physiologic mechanisms and ultrastructure in order to depict a personal view of pulmonary edema and water exchange in the lungs. It is not a comprehensive survey; for this the reader is referred elsewhere. Instead, by using the traditional concepts of hemodynamic and permeability pulmonary edema as contraposts, it will attempt to provide a general scheme to which the various forms of clinical pulmonary edema can be related.

General Considerations

Functional Anatomy of the Alveolar-Capillary Interfaces

Fluid exchange in the lungs occurs in the vicinity of gas exchange. Relationships between structures that are involved in both processes may be best appreciated in an edge-on view of the alveolar septum (fig. 1). Capillaries, no different from those found in muscle, are eccentrically incorporated into the alveolar septum so that three distinct functional zones may be identified: a thin side of the alveolar-capillary barrier for gas exchange, and a thick side, which serves both for support and for water exchange (fig. 2). The relative thickness of the two sides depends on the amount of interstitial space that each includes between its endothelial and epithelial aspects.

Thick Side for Support

Included in the thick aspect are collagen and elastic fibers, fibroblasts, and macrophages, i.e. the terminal extensions of the connective-tissue skeleton of the lobe. Between the endothelial and alveolar basement membranes of this part of the septum lies the interstitial space, containing a ground substance of polymerized hyaluronic acid and other mucopolysaccharides in addition to the connective-tissue elements. The role of the
Edge-on view of the alveolar-capillary membrane. Electron microphotograph showing three capillaries (C) suspended in the septum between alveoli (ALV). On the right side of the middle capillary, the alveolar septum is thin; the opposite side is thick containing supporting elements, including collagen fibers (CF) in the interstitial space between the capillary and alveolar basement membranes. Section stained with uranyl acetate and lead citrate, × 10,000.
interstitial space in water exchange will be considered subsequently.

Thin Side for Gas Exchange

The capillary network is suspended on either side of the alveolar-septal wall, beneath the alveolar surface. In figure 1, the thin aspect of the capillary wall is seen bulging into the alveolus. In contrast to the opposite thick side, the interstitial space on the bulging side is exceedingly thin (300–500 Å) consisting of fused alveolar and endothelial basement membranes. Accordingly, the thin side of the alveolar-capillary septum is made up of only three anatomic layers (alveolar epithelium, capillary endothelium, and their fused basement membranes), an arrangement which provides the lungs with an enormous expanse for gas exchange without the encumbrance of excessive mass. Clearly, for the thin side of the capillary wall to function effectively in gas exchange, it must not thicken unduly and it must resist the passage of water into alveoli. The ultrastructural design of the alveolar septum provides for this contingency by including preferential channels which direct excess water to the thick side for disposal.

Thick Side for Water Exchange

It has been noted above that the thick side contains a wide interstitial space between the basement membranes. Consequently, five discrete layers separate alveolar air from capillary blood in this region of the alveolar-capillary barrier: alveolar epithelium, basement membrane, interstitial space, basement membrane, and capillary endothelium. By this construction, the thick side of the alveolar-capillary membrane not only provides support for the capillary network, but is also an essential component of the water-exchanging apparatus of the lung, operating to expedite the exit of water and protein from the interstitial space of the alveolar septum toward lymphatic capillaries and interstitial spaces elsewhere. Indeed, the system for dispatching excess water from the alveolar septum is so efficient that fluid accumulation may be most marked in remote interstitial spaces around large vessels and bronchi even though it gained access to the interstitial space via alveolar-capillary walls.

With respect to permeability, the alveolar-capillary membrane behaves like a cell membrane rather than like a conventional muscle capillary. Since the alveolar capillary has no distinctive anatomic or functional features, it is reasonable to conclude that any special behavior with respect to passage of water, electrolytes, or colloids is attributable to the alveolar rather than to the endothelial components.

Interstitial Edema

Figure 3 illustrates the ultrastructural localization of pericapillary interstitial edema produced experimentally by a combination of increased pulmonary capillary pressure and hemodilution. The thick side of the capillary wall is widened and the collagen fibers are separated presumably by imbibition of water. However, the thin side of the capillary is not expanded, preserving its structure for gas exchange. It should be noted that such changes are not detectable by conventional histologic technics.

Surfactant

Not shown in figures 1 and 2 is an amorphous biochemical layer that lines the alveoli. In this layer is a lipoprotein complex,
Interstitial pulmonary edema. The interstitial space (IS) of the thick portion of the alveolar septum has been considerably widened by edema fluid during hemodynamic pulmonary edema whereas the opposite thin part, containing the fused basement membranes (BM), remains unchanged in thickness. In the alveoli, surrounding the red blood cell (RBC) in the capillary,
"Surfactant," which is synthesized locally by alveolar type II cells. This complex exerts an "antiatelectasis" effect, stabilizing alveoli and preventing surface forces at their air-water interfaces from collapsing them under conditions of low alveolar volume. The significance of this layer with respect to water exchange will be considered subsequently.

"I-Receptors"

Paintal has recently described specialized juxtaalveolar capillary receptors ("I-receptors") in the interstitial space adjacent to collagen. These have been depicted as stretch receptors that are stimulated by the deformation associated with an increase in pericapillary interstitial volume. Consequently, these receptors are in a position to sense excess water in the pericapillary interstitial space and to stimulate increased ventilatory activity which, in turn, promotes the removal of excess water from the lungs via the lymphatics.

**Extraalveolar Vessels**

In the pulmonary circulation thin-walled minute vessels, larger than capillaries, do participate in gas exchange. Therefore, it would not be surprising if minute pulmonary vessels, somewhat larger and thicker than capillaries, were also involved in water exchange. Indeed, the possibility has even been raised that precapillary vessels of the order of 1000 µ in diameter may leak directly into their surrounding perivascular spaces if conditions are right. However, these provocative experiments have not yet settled the route by which excess water that was demonstrated histologically gained access to the interstitial space around large vessels and airways: through normal, transvascular channels, by subtle disruptions of vascular walls, or by conventional translocation of water from the pericapillary to periarterial and peribronchial interstitial spaces.

**Lymphatics**

The lungs are pervaded by an extensive network of lymphatics. They begin as lymphatic capillaries in the vicinity of the alveolar ducts and form a racemosing "third circulation" within the connective-tissue framework. Water and protein are moved from the pericapillary space toward the lymphatic capillaries and perivascular interstitial spaces by gradients of subatmospheric pressure. Once in the larger lymphatics or in the interstitial spaces around larger vessels or airways, water and protein are advanced toward the hilus primarily by the ventilatory movements.

In acute experimental pulmonary edema, there is a delay between the entry of excess water into the interstitial space and increased lymphatic flow measured at the exit from the thorax by cannulating the right lymphatic duct. Two mechanisms seem to account for the delay: (1) the retention of excess water by the ground substance and collagen in the interstitial space until it is cleared from the alveolar septum, and (2) the large capacity of the intrapulmonary lymphatics.

Many questions remain about the structure and function of the pulmonary lymphatic system. For example, it is difficult to rationalize the function of the extensive pulmonary lymphatic network if, as generally believed, the net flux of water across the pulmonary capillaries is such that only small quantities are left behind in the pericapillary space for removal. This discrepancy between the amount of water to be drained and the capacious drainage system has strengthened the idea that the major role of the pulmonary lymphatics is to return protein, rather than water, to the systemic circulation; this removal of protein is imperative if the balance of forces regulating water movement across the capillary wall is to continue to operate.

It may seem curious that excess water should ever accumulate in the lungs in the...
face of such an elaborate drainage system. The solution to this dilemma, originally advanced by Drinker on the basis of animal experiments and supported by more recent observations on man, seems to be that the ceiling for lymphatic drainage is set by the relatively small calibers of the thoracic and right lymphatic ducts ("exit lymphatics"). In chronic left ventricular failure, the entire lymphatic system proliferates and the exit lymphatics increase in caliber. Nonetheless, enlargement of the exit lymphatics apparently remains inadequate to keep the lungs free of excess water.

Systemic venous hypertension, as seen in patients with isolated right ventricular failure, does not impede the outflow of lymph from the lungs enough to make excess water in the lung a clinical problem. Presumably, the combination of tachypneic ventilatory movements and muscular constriction of the walls of the large lymphatics suffices to keep the lungs free of edema; whether extraordinary levels of venous pressure, such as occur when tricuspid valvular insufficiency supervenes, can also be discounted, is unknown. On the other hand, in disorders of the left side of the heart that increase the entry of water into the interstitial space, clinical pulmonary edema may be abetted by systemic venous hypertension and the impediment that it affords to lymphatic drainage.

**Hypercapnia in Pulmonary Edema**

Clinicians have recently been alerted to the prospect of CO₂ retention in pulmonary edema. The anatomic considerations presented above provide a basis for predicting when this will occur. Thus, during the phase of interstitial and alveolar edema, which is generally spotty in distribution, reflex hyperventilation from the stiff lungs (possibly because of the "J-receptors") would be against an increase in arterial PCO₂. But, if edema overflows the alveoli in sufficient quantity to obstruct terminal bronchioles, CO₂ elimination would be expected to be impaired, consequent to ventilation-perfusion abnormality rather than to impaired diffusion. If ventilation is no longer sustained at a high level, because of exhaustion or respiratory depressants, the prospects for hypercapnia are enhanced. Other imbalances, such as the metabolic alkalosis induced by potent diuretics, may also contribute to the hypercapnia. But, despite this variety of possibilities, hypercapnia is an unlikely occurrence until water has accumulated to the point of obstructing terminal airways, or ventilatory depression advance.

**Forces Involved in Pulmonary Edema**

Starling pictured the exchange of water and solutes across capillary walls as though the barrier were inert and the passage of water and solutes were determined entirely by physical and physicochemical forces. These forces are summarized in figure 4.

**Intravascular and Interstitial Pressures**

It is well known that the rate of accumulation of fluid in the lungs is influenced by the difference between capillary hydrostatic pressure and the osmotic pressure of the plasma proteins. Indeed, for a while it was believed that vascular pressures could, per se, account for observed rates of water accumulation.
However, the relationship has since proved to be nonlinear, thereby emphasizing that other forces are involved. Nor is the rate of water accumulation fully accounted for by the other forces in the Starling equation, i.e., interstitial hydrostatic and oncotic pressures.28

Part of the discrepant behavior of the lungs with respect to water accumulation seems attributable to the layer of surfactant lining the alveoli. As long as this layer is intact, increasing airway pressures do not impede water accumulation in the lung in experimental animals that have been predisposed to develop pulmonary edema because of high pulmonary capillary pressures and low osmotic pressure of serum proteins. Removal of this layer by saline lavage of the lungs does result in a striking decrease in the rate of water accumulation as airway pressures are raised29

This sequence suggests that surfactant ordinarily stands as a barrier between the interstitial space and imposed airway pressures. As a corollary, the success of positive-pressure breathing in decreasing pulmonary edema seems more attributable to its phlebotomy effect on systemic venous return to the lungs than to its antiedema effects on the pulmonary capillaries.

**Interstitial Edema**

The ease with which water collects in the pericapillary interstitial space depends on the amount of water that is already there. As long as the water content and pressure in the pericapillary interstitial space are normal, water does not accumulate readily. Ordinarily, pericapillary pressures that determine water exchange in the lung are subatmospheric.9, 13, 29

Then, when enough water has accumulated in the pericapillary interstitial space to raise pericapillary pressures to atmospheric and above, additional water is more readily accommodated, i.e., large increments in water content of the interstitial space are accompanied by small increments in interstitial fluid pressure ("high compliance"). Unfortunately, the experiments that have demonstrated the changing pressure-volume relationships that accompany changes in the hydration of the interstitial space have left unsettled whether the increase in compliance represents a dramatic change in the physical characteristics of the pericapillary interstitium, or simply marks the overflow of fluid into alveolar spaces. Nonetheless, the clinical implication seems to be that excess water in the lungs potentiates the accumulation of more water, i.e., edema begets edema.

Because the interstitial space is continuous and under the influence of gravity, water seeps to the bottom of the lungs so that interstitial-fluid pressures are higher at the bottom than at the top of the lung. Also, forces at the surface of the lung are nonuniformly transmitted within its substance so that the interstitial pressures involved in water exchange are more subatmospheric around extraalveolar vessels than around pulmonary capillaries.29-31

That these irregularities in interstitial-fluid pressure influence local water exchange and pericapillary protein concentrations seems self-evident. Indeed, it is tempting to attribute some of the patchy patterns of acute pulmonary edema encountered clinically to such nonuniform interstitial pressures. On the other hand, even if pulmonary edema is originally spotty, in time the excess water tends to pool in the dependent areas of the lungs unless some local mechanism, such as lymphatic obstruction by fibrosis, arrests it, or unless heightened ventilatory efforts direct it, via lymphatic channels, toward systemic veins.

**Quantitative Assessment of Pulmonary Edema**

It was noted above that traditional clinical hallmarks of pulmonary edema, i.e., dyspnea, orthopnea, rales, frothy fluid in airways, or roentgenographic changes, signify an advanced rather than an incipient state of excess water in the lungs.14, 32 Even at autopsy, recognition of early pulmonary edema may be difficult particularly when pulmonary congestion is also present to blur the boundaries between expanded vascular and extravascular volumes. Totally unreliable is the distribution of the pulmonary edema which is regularly modified, to an unpredictable extent, by the effects of gravity and the time that elapses.
between death and autopsy. Finally, histologic examination is compromised by the inability to identify water except by the proteinaceous silt which it leaves behind or by the deformities that it produces in cells and tissues.

These practical limitations have stimulated interest in objective estimates of the amount of water in the lungs during normal and abnormal conditions. The most direct approach has been the double indicator-dilution technic of Chinard and Enns.21 Less direct have been the attempts to identify and to characterize derangements in pulmonary mechanics.

*Extravascular Water Volume by Indicator-Dilution Technic*

With Evans Blue (T-1824) and tritiated water as indicators, the extravascular water content of the lungs has been estimated both in animals and man.2, 3, 14, 33 The method measures a fixed fraction of the total extravascular water of all parts of the lungs that are perfused. Although values for this fraction have varied somewhat from laboratory to laboratory (50–65% of total lung water), each laboratory reports satisfaction with its own consistency. An important restriction in the use of serial determinations during changing hemodynamic conditions is that the same areas of the lung be represented in the consecutive measurements. For example, in hypotensive states, in which pulmonary apices may be hypoperfused, the water space of the apices will not be measured.34

*Pulmonary Performance in Pulmonary Edema*

The stiff edematous lung does inordinate work and expends excessive energy in breathing.32 Generally the excess water is shared between the vascular and extravascular compartments. This excess fluid is accommodated at the expense of the alveolar volume, not only by direct encroachment and altered distensibility but also by promoting alveolar closure as surfactant is displaced or rendered ineffective.35

For years, serial determinations of vital capacity have been used as an empirical gauge of the course of fluid accumulation in the lungs in left ventricular failure. Recently, more quantitative and meaningful information concerning the mechanical performance of the lung has been obtained from determinations of pulmonary compliance and of airway resistance. However, neither mechanics nor lung volumes distinguish reliably between congestion and edema.2 Even though quantitative measurements are still difficult to interpret in absolute terms, serial determinations may be useful in tracing the response to therapy.

**Hemodynamic Pulmonary Edema**

In a previous section it was noted that there is little experimental support for the prevalent notion that the rate of accumulation of excess water in the lungs is linearly related to the increase in pulmonary capillary pressure (even if plasma proteins are normal). Among the evidence cited to the contrary were the influence of interstitial hydrostatic and oncotic pressures, the complicated pressure-volume relationships of the pericapillary interstitial space of the lungs, and the uncertain performance of the lymphatic circulation. The experimental work referred to2, 9, 33 consistently used an increase in left atrial and pulmonary venous pressure (as might occur in left ventricular failure or mitral valvular disease) as the device to increase pulmonary capillary pressures. The present section will consider the possible role of pulmonary arterial hypertension, rather than pulmonary venous hypertension, in causing pulmonary capillary hypertension and pulmonary edema.

**Distribution of Pulmonary Edema**

The distribution of pulmonary edema during life is currently assessed by roentgenograms. As displayed by this technic, pulmonary edema is rarely uniform. Sometimes, particularly in chronic left ventricular failure, water has gravitated to the lung bases. Other times, especially soon after onset, the pattern may be "bat wing" or "butterfly" in distribution, so that the central portions of the lungs appear to be markedly edematous whereas the peripheral lower and apical parts of the lungs

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appear to be spared.\textsuperscript{36, 37} Originally this pattern was considered to be the hallmark of "uremic pulmonary edema." In time, this pattern has proved to be much less specific.

Of the various mechanisms to which the "butterfly" pattern has been attributed, least debatable is the architectural difference between the hilar and peripheral portions of the lungs. This difference is so striking that some investigators have pictured the lung in terms of a kidney and have even described a "medulla" and "cortex."\textsuperscript{36-38} The distinctive anatomy, in turn, has been held responsible for characteristic inhomogeneities in ventilation and lymphatic flow which could contribute to preferential localization of edema in the vicinity of the hilum of the lung.

Although the picture of the lung as a kidney is undoubtedly somewhat exaggerated, the anatomic inhomogeneities are undeniable. Not only do they suggest mechanisms by which drainage from the lung may be impaired, thereby favoring central stasis and accumulation of water, but they also encourage the notion that more water may be liberated into the interstitial spaces of the central than of the peripheral portions. For example, shorter path lengths of precapillary vessels near the hilus could favor central edema by predisposing to higher capillary pressures in the central than in peripheral portions of the lungs.

Our laboratory explored the possibility that precapillary resistances might not be uniform throughout the lungs.\textsuperscript{39} Using the intact, unanesthetized rabbit we found a remarkable redistribution in response to a variety of experimental manipulations and were able to induce preferential slowing of blood flow in some areas (regional vasoconstriction) while blood flow elsewhere in the lung was accelerating (regional vasodilatation). The implication of this observation for the genesis of pulmonary edema is that the transmission of pulmonary arterial pressure to pulmonary capillaries need not be uniform, and that areas of relative precapillary vasodilatation may contribute to regional pulmonary edema. In the section that follows, this possibility is illustrated with particular reference to the genesis of high-altitude pulmonary edema.

**Acute Pulmonary Edema of High Altitude**

In the 35 years since Hurtado's original description,\textsuperscript{40} this clinical syndrome has become well known. The prototype is the young, healthy, native resident of high altitude who returns home after a brief holiday at sea level only to experience, without apparent cause, life-threatening pulmonary edema. The equivalent syndrome for sea-level dwellers occurs in the young or middle-aged physician who, after an interlude of sedentary existence, takes a skiing holiday at altitude: he ascends rapidly, indulges unreservedly in strenuous exercise, retires for the night somewhat exhausted but reassured of his physical prowess, only to be reawakened by flooded lungs.\textsuperscript{41, 42}

The pathogenetic sequence presumably starts with a constitutionally predisposed individual who develops an inordinate degree of pulmonary arterial hypertension when exposed to tolerable levels of hypoxia. An additional prerequisite is regional inhomogeneities in pulmonary capillary pressures due to nonuniform populations of precapillary resistances so that the extraordinary pulmonary arterial hypertension affects some pulmonary capillary pressures more than others. The missing link in this postulated sequence is how the nonuniform transmission of pulmonary arterial pressure to the pulmonary capillary bed is effected. Viswanathan, Jain, and Subramanian have proposed a combination of mechanisms including "severe contraction of muscular arterioles (which) results in wider opening of perpendicular muscular arterioles," increased capillary permeability and luminal occlusions distal to spastic arterioles.\textsuperscript{45} To account for nonuniform intensity of precapillary vasoconstriction upon return to altitude, Viswanathan and associates have also proposed that the hypertrophied muscle of the high-altitude native involutes nonuniformly during his stay at sea level. Although the anatomic bases for the patchy pulmonary edema of high altitude remain to be clarified, the functional concept of nonhomogeneous
distribution of precapillary resistances has emerged as a useful guiding principle in the pathogenesis of the disorder.

Gravity in Localizing Pulmonary Edema

Although the effects of gravity on the distribution of blood flow and ventilation in the normal lung are quite clear, its effects on the distribution of acute pulmonary edema are more difficult to predict. On the one hand, gravity predisposes to dependent edema not only by generating higher hydrostatic pressures toward the bases than at the apices, but also by draining interstitial fluid toward the bases via the continuous interstitial spaces; incompetent lymphatic valves contribute to dependent interstitial edema. On the other hand, augmented (reflex) ventilatory movements during pulmonary edema promote the removal of fluid from the lungs via the lymphatics. Between these opposing influences are the important mechanical effects that edema exerts locally by modifying local interstitial pressures; it may also affect capillary hydrostatic pressures by decreasing the caliber of precapillary vessels. The net effect of these opposing influences is a wide, and unpredictable, range of pulmonary capillary and interstitial pressures in the lungs, particularly if protein-rich fluid stagnates in the interstitial space, and mechanical forces are misdirected because of local fibrosis.

Permeability Pulmonary Edema

Physiologic observations indicate that the alveolar epithelium is the least permeable component of the alveolar-capillary barrier, suggesting that interstitial edema and increased pulmonary lymphatic flow are regular antecedents of alveolar edema. One possible interpretation of these observations is that alveolar edema is a sequel to combined inadequacy of the reservoir function of the pulmonary interstitial space and the drainage function of the pulmonary lymphatics. As a corollary, alveolar edema can only be regarded as a late sign of excess water in the lungs. Moreover, increased pulmonary lymphatic flow need not be a reliable criterion that excess water is accumulating in the lungs even though it can be used to signify an increased rate of entry of water into the pulmonary interstitium (assuming that ventilation and experimental conditions remain unchanged).

In recent years, ultrastructural observations have provided strong morphologic support for the physiologic conclusions concerning permeability.

Pulmonary Capillaries

Electon microscopy of pulmonary capillaries has revealed a remarkably complicated structure even though they behave physiologically as though they were simple semipermeable membranes. Of particular interest with respect to permeability are the clefts between endothelial cells (approximately 200 A wide) which are narrowed at irregular distances from their capillary ostia to form "pores" or "junctions" corresponding to slits 40-50 A wide. Presumably, the entire endothelial surface is available for the movement of water, and of lipid-soluble substances. But, lipid-insoluble substances seem to traverse the endothelial wall via the endothelial clefts. Furthermore, because of the "pores" within the clefts, sieving occurs due, in large part, to molecular dimensions. Thus, large molecules (mol wt > 90,000) are arrested whereas smaller molecules (mol wt > 10,000) are sieved along the way. The sites of narrowing ("pores" or "junctions") have been identified as the "morphologic equivalent of small pores" postulated by physiologists, both with respect to their dimensions and the area of capillary surface that they occupy.

How the larger molecules (mol wt > 90,000) cross the endothelium is much less certain: some investigators postulate the existence of a large "pore" system, consisting of few, exceedingly large "leaks" (1-20 "leaks"/100,000 pores). Others favor transport across the endothelium by vesicles ("pinocytosis"). At the present time there is no way to resolve the dilemma of the large pores. However, our own experience, using tracers in the pulmonary circulation, supports the idea that the small pores (junctions) play an important role in determining the transport of...
lipid-insoluble molecules across the endothelium of the pulmonary capillaries.  

The dimensions of the small pores (junctions) are not fixed. Indeed, in the pulmonary capillary they seem to be strongly influenced by hydrostatic pressures, at pulmonary capillary pressures of less than 50 mm Hg, they arrest inert tracers such as stroma-free hemoglobin (mol wt 64,000, radius about 30 Å; fig. 5). At higher intraluminal pressure, however, the pores stretch, allowing the tracer to pour into the interstitial space (fig. 6). Obviously, the concept of stretchable pores blurs distinctions between large and small pores. It also undermines distinctions between hemodynamic and permeability pulmonary edema since the elevated hydrostatic pressures cause the pulmonary capillaries to become leaky. Moreover, once colloidal molecules enter the interstitium, the tendency for water to flow out of the vessel is enhanced.

Relative Permeabilities

In 1930 Rous, Gelding, and Smith, using diffusible dyes injected intravenously, adduced evidence for a greater permeability of the venular than of the arteriolar portions of the systemic capillary bed. Indeed, in the systemic circulation, permeability increases down the vascular tree so that venules and veins are more permeable than capillaries and arterioles.

Applying this approach to the lungs, Boehm found in rats that preferential pulmonary vascular leakage did occur during pulmonary edema, the site varying with the agent that he used to induce edema. Others, using different approaches, have also shown that pulmonary vessels other than capillaries can leak, but the question of relative permeabilities is still in its infancy with respect to the lungs, and the extent to which this phenomenon influences the distribution of fluid in

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Figure 5

Dog lung perfused at normal pulmonary arterial pressure for 20 min. In this peroxidase-reacted section, the reaction product of stroma-free hemoglobin (Hb) fills the capillary lumen and is arrested by the junction (J) in the cleft between two endothelial cells (End). Also shown are pinocytotic vesicles (Pv) apparently free in the cytoplasm, filled with the hemoglobin-reaction product. Unstained section reacted with peroxidase, ∞ 120,000.
Figure 6

Dog lung perfused at high pulmonary arterial pressure (50 mm Hg) for 20 min. (Top) The reaction product of the stroma-free hemoglobin fills the lumen (L) of the capillary and extends via the clefts between adjacent capillary endothelial cells (END) and stains the basement membrane (BM). The vicinity of the junction (J) is also indicated. Unstained section reacted with peroxidase, × 120,000. (Bottom) As the high pulmonary arterial pressure is sustained, the tracer extends into the cleft between alveolar epithelial cells (Ep) to be arrested at the "tight" alveolar junction (J). The collagen fibers in the interstitial space are outlined by the hemoglobin. Unstained section reacted with peroxidase, × 32,000.

various types of pulmonary edema is as yet unclear.

Leaky Bronchial Venules

Many years ago, Miller called attention to the complex network of bronchial venules that coursed along the entire length of the
bronchial tree.\textsuperscript{17} This arrangement, illustrated in figure 7, depicts the bronchial muscle interposed between the submucosal and the subadventitial components of the venous system; many venous links bridge the muscle. It is easy to imagine an important physiologic function, such as the warming of inspired air, for this elaborate venous network, but as yet only a pathophysiologic role has been suggested. Thus, Pietra and his associates have shown that histamine, by any route of administration—airways, intravenously, or subcutaneous injection—selectively causes bronchial venules to leak, i.e. produces interstitial edema,\textsuperscript{56} while leaving pulmonary vascular permeability unaffected (fig. 8). In essence, histamine selectively causes the systemic venules of the lung to leak. Bradykinin elicits the same response. The anatomic basis for this selective response is not entirely settled. One attractive prospect is that this specialized response is caused by contractile filaments in the endothelium of the bronchial venules. Within the lung, these seem to be unique to bronchial venules. Similar cellular components, as well as contractile proteins,\textsuperscript{57, 58} have been identified in systemic endothelium. For example, Majno, Shea, and Leventhal implicated them in the selective leakage of venules after topical application of histamine to the cremaster muscle.\textsuperscript{58} Whether these contractile elements are the explanation for preferential bronchial venular leakage after histamine and bradykinin is currently under investigation.

**Hypoxia**

Drinker, relying heavily on serial measurements of lymph flow, stressed the importance of hypoxia in causing fluid-exchanging vessels in the lungs to leak.\textsuperscript{59} Subsequent investigators,\textsuperscript{60, 61} using different technics, have provided no support for Drinker’s view. Indeed, the current consensus is overwhelmingly opposed to an important role for hypoxia in the genesis of pulmonary edema. Nonetheless, some basis remains for leaving the question open. Theoretically, as pulmonary arterial pressures increase during hypoxia, tracers would be expected to cross endothelial walls through channels that had previously been closed to them (fig. 6); i.e., permeability increases and increased lymphatic flow would be expected even though clinical pulmonary edema does not occur.\textsuperscript{62} Besides, we have observed in the clinic that severe hypoxia, especially in association with respiratory acidosis, may be associated with pulmonary edema despite normal left heart pressures.

These observations suggest that in the normal lung that is adequately ventilated acute hypoxia increases the rate at which water enters and leaves the interstitial space. Presumably, the same phenomenon was observed by Drinker using lymphatic cannulation\textsuperscript{59} rather than inert tracers. Should severe hypoxia persist, interstitial and even alveolar edema may succeed the stage of alveolar-capillary leakage and increased lymphatic outflow.

**Pharmacologic Agents**

Continued exposure to oxygen-rich environments operates subtly but inexorably to cause pulmonary edema.\textsuperscript{63} Toxic inhalants, such as chlorine, phosgene, or nitrogen dioxide, act more dramatically. Attention has focused on injury to the endothelial components of the

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**Figure 7**

Schematic representation of bronchial venular plexus. The bronchial arteries (BA) deliver blood to the bronchial venular plexus, part of which lies beneath the mucosa and part beneath the adventitia. Between the two components of the plexus lies the bronchial muscle. Connecting links are shown between the submucosal and subadventitial components. Blood leaves the venous plexus via bronchial veins (BV).
Histamine on bronchial venules. Ten minutes after the subpleural injection of histamine, carbon (C) that had been injected intravenously, is shown on both sides of the endothelial cells. Some carbon (C) remains in the capillary lumen which contains red blood cells (RBC). This carbon is in the vicinity of an endothelial cleft and junction (J). Carbon has also entered the interstitial space where it is between the endothelium and a pericyte. Section stained with uranyl acetate and lead citrate, $\times$ 10,000.

alveolar-capillary membranes as the mechanism for these inhalant types of pulmonary edema. However, the possibility remains that the submucosal bronchial venous plexus may also be injured, thereby contributing to the interstitial edema surrounding larger vessels and airways: the bronchial venular plexus (described above) lies subadjacent to the bronchial mucosa; gases, such as nitrogen dioxide, are quite soluble in water so that they may gain direct access to the submucosal bronchial venular plexus during breathing.

The residual effects of these toxic inhalants also dramatize the consequences of the more conventional and insidious forms of pulmonary edema. Thus, after nitrogen dioxide inhalation, organization and fibrosis may be quite striking, presumably due to the over-
whelming of fibrinolytic mechanisms by inordinate quantities of fibrinogen in the interstitial and alveolar spaces. The same process, operating at a much slower rate, may contribute to the perivascular fibrosis of chronic pulmonary congestion and edema.64 Conversely, fibrinogen-poor material in the interstitial and alveolar parts of the lung (as in alveolar proteinosis) stimulate much less fibrosis.

“Shock Lung”

This unsatisfactory rubric has been applied to a life-threatening sequence of respiratory distress and insufficiency that follows nonthoracic trauma.65 Pulmonary edema is a regular pathologic component of this syndrome. In Vietnam, the usual succession of events terminating in shock lung is as follows: A wounded soldier is successfully treated in the field for hemorrhage and hypotension and is evacuated to the base hospital. While convalescing, often without warning, he develops dyspnea and tachypnea, and soon progresses to cyanosis and overt respiratory insufficiency. At first, X-rays of the chest show scattered, mottled densities in both lungs; but, in short order, the shadows become confluent toward the lung bases. Physiologic measurements show that the lungs are stiff and the arterial blood is hypoxemic and hypocapniae, reflecting a combined respiratory alkalosis and metabolic acidosis.66

The same clinical picture occurs in civilian life and is either categorized vaguely as “adult respiratory distress syndrome” or identified according to etiology: extracorporeal oxygenation; fat emboli; overtransfusion after an episode of hypotension; prolonged breathing of enriched-oxygen mixtures; aspiration of gastric contents; certain viral infections of the lungs; and even therapeutic radiation of the thorax for malignancy. At autopsy, the regular features include edema, congestion, and atelectasis, leading to the anatomic designation “congestive atelectasis.” The common anatomic features despite the varieties of initiating mechanisms suggest that the anatomic expression of the response of the lung to injury is exceedingly stereotyped. That large alveolar-capillary leaks contribute to the syndrome is suggested by the accumulation of large proteins, such as fibrinogen, in the alveoli.64

Although it may be misleading to generalize about the pathogenesis of “shock lung,” it would be an oversight to ignore the clinical syndrome of “shock lung,” that follows a period of systemic hypotension and transfusions: during the period of systemic hypotension, parts of the lung are hypoperfused,67 treatment generally involves transfusions, particularly of crystalloidal solutions. It seems reasonable to attribute the pulmonary edema after recovery from the hypotensive state to a combination of leaky pulmonary vessels and overhydration. That arrest of pulmonary blood flow damages the lungs is well known; even more familiar is the overexpansion of the blood volume and extracellular fluid volumes that may complicate overzealous administration of noncolloidal solutions, particularly when restoration of the elaborately controlled systemic arterial blood pressure is the major guide to the quantity of transfused fluid.

Overdosage of Narcotic Agents

Pulmonary edema may complicate an overdose of heroin or methadone. In one characteristic syndrome, the patient is comatose, severely hypoxemic, and in respiratory acidosis because of severe ventilatory depression. On X-ray, the pulmonary edema is nonuniform in distribution. There are three popular explanations for the patchy pulmonary edema: (1) leakage of pulmonary capillaries (or other minute vessels of the lungs) effected by hypoxemia and acidosis, (2) left ventricular failure, and (3) leakage of pulmonary capillaries due to a direct noxious effect of heroin (or a contaminant injected simultaneously).68 Of the three, left ventricular failure is to be expected if hypoxemia (and acidosis) is sufficiently severe to compromise myocardial performance. Conversely, a unique effect of the narcotic agent in promoting capillary leakage seems unlikely since heroin, methadone, and other respiratory depressants,
or barbiturates, may also cause pulmonary edema. In previous sections we have reviewed the basis for our view that severe hypoxia promotes leakage of pulmonary capillaries and emphasized the important role of adequate ventilation in ensuring lymph flow from the lungs.

Accordingly, the pathogenetic mechanisms that have been considered in previous sections seem to be operative in narcotic pulmonary edema associated with coma: pulmonary capillary hypertension (from left ventricular failure, and nonuniform transmission to the pulmonary capillaries of pulmonary arterial hypertension elicited by hypoxemia and acidosis), leaky pulmonary capillaries (from hypoxemia and possibly acidosis), and impaired lymphatic drainage (from depressed ventilation).

It is certain that not all types of narcotic pulmonary edema share this pathogenesis. Indeed, there is a strong likelihood that “street heroin” may include contaminants that are capable of exerting noxious effects of their own. Nonetheless, the prompt improvement of the patient with narcotic pulmonary edema and coma in response to assisted ventilation and adequate oxygenation emphasizes the likelihood that the pathogenetic sequence outlined above may apply. It also encourages further attempts to divest unconventional types of clinical pulmonary edema of their aura of mystery by considering pulmonary edema in terms of those mechanisms which ordinarily operate to maintain water (and protein) balance in the lungs and of derangements in the balance of these mechanisms which lead to the accumulation of excess water (and protein) in the lungs.

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References

1. Fishman AP, Becker EL, Fritts HW Jr, Heinemann HO: Apparent volumes of distribution of water, electrolytes and hemoglobin within the lung. Amer J Physiol 188: 93, 1957

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22. MILLER WS: Distribution of lymphoid tissue in the lung. Anat Rec 5: 99, 1911
34. LEVINE OR, MELLINS RB, SENIOR RM: Extravascular lung water and distribution of pulmonary blood flow in the dog. J Appl Physiol 26: 166, 1970
38. FLEISCHNER FG: The butterfly pattern of acute pulmonary edema. Amer J Cardiol 20: 39, 1967
42. PEÑALOZA D, SIME F: Chronic cor pulmonale due to loss of altitude acclimatization (chronic mountain sickness). Amer J Med 50: 728, 1971
44. WEST JB: Regional differences in blood flow and ventilation in the lung. In Advances in Respiratory Physiology, edited by Card CG. Baltimore, Williams & Wilkins, 1966, p 198


51. **Pietra GG, Szidon JP, Leventhal MM, Fishman AP**: Hemoglobin as a tracer in hemodynamic pulmonary edema. Science 166: 1643, 1969


57. **Becker CG, Murphy GE**: Demonstration of contractile protein in endothelium and cells of the heart valves, endocardium, intima, arteriosclerotic plaques, and Aschoff bodies of rheumatic heart disease. Amer J Path 55: 1, 1969


59. **Drinker CK**: Pulmonary Edema and Inflammation. Boston, Harvard University Press, 1945


63. **Clark JM, Lambertsen CJ**: Pulmonary oxygen toxicity: A review. Pharmacol Rev 23: 37, 1971


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