gradients appear inadequate to account for considerable transfer of fluid into or out of the pleura ; the presence of a more permeable membrane of a larger surface area is indicated. This surface may include the venules and perhaps even a segment of the venous end of the capillaries. The markedly enhanced filtration of fluid when venous pressure is elevated suggests that the venous end of the capillaries may be the permeable membrane. This point of view is supported by the increase in fluid transfer during retrograde perfusion of the lung lobe, compared with antegrade perfusion.

Airway Space

The absence of filtration at pressures lower than the threshold (12 cm H₂O) suggests the possibility that a hydrophobic (lipid?) surface cover inhibits filtration across the alveolar capillaries. The threshold for airway filtration at about 14 cm. RL suggests that a critical change occurs in the airway vessels at this point. This may result from abnormal distention (ballooning) of the alveolar capillaries as well as the simultaneous thinning of these vessels would facilitate the rate of filtration.

SUMMARY

Filtration patterns from the pulmonary vascular bed into the pleural space differ from those for the airway spaces. In the pleural space, the direction and the rate of filtration are proportional to the vascular-pleural pressure differences. Filtration into the airway is inhibited as long as vascular pressure exceeds airway pressure by less than 12 cm. H₂O. At higher transmural pressures filtration is very rapid. Retrograde perfusion produces more filtration than antegrade perfusion. These data suggest that the transmural filtration occurs at the venous end of the capillaries and perhaps in the venules. A special property of the airway prevents filtration until a critical value is achieved. The significance of these filtration patterns in ventilation, effusion and edema are discussed.

Lymph Formation in the Lungs

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The lymphatic vessels return to the blood stream excess tissue fluid and, more particularly, remove large protein molecules and particulate matter from the interstitial fluid. Since such extravascular macromolecules readily enter the lymphatic capillaries, it is reasonable to consider lymph to be similar in composition to the tissue fluid of the same region. Although there may be in certain tissues some exchange of protein molecules with the cells, the concentration of protein in the tissue fluid and lymph is determined largely by the degree of filtration through the blood capillaries. This will depend on the fine structure of these vessels and on the haemodynamics of the particular region.¹⁾

In studying the rôle of the lymphatics in the body, therefore, we should con-

sider an intravascular pool of plasma protein, in man about 200 Gm., and several extravascular pools, each varying considerably in size but also amounting in total to about 200 Gm. The leakage of protein from the intravascular pool to the extravascular pools and its return via the lymphatic vessels also varies considerably, depending not only on the fine structure of the blood capillaries and on the local hemodynamics, but also on the size of the pool in each particular region. The total exchange or extravascular circulation of plasma protein, while small in relation to the intravascular circulation, amounts during the course of a day to about 100 to 200 Gm. in man, i.e. 50 to 100% of the protein in the circulating plasma.

The anatomical relationships concerned in lymph formation in the lung

In the lung the blood in the capillaries is in very close proximity to the air in the alveoli to ensure the rapid exchange of gases between the atmosphere and the blood. This alveolar air-blood barrier consists of 2 continuous cellular membranes supported by a basement membrane. Electron microscopy has shown that the capillary endothelium is a continuous membrane consisting of typical nucleated endothelial cells which have a maximum thickness of 2μ . in the region of the nucleus but which attenuate to a thin sheet, in some areas reaching a minimum thickness of only $10\text{ m}\mu$. ($100\text{ \AA}$). Adjacent cells are closely bonded together, the junctions being about $100\text{ \AA}$ across, without any gaps and the endothelium is supported by a basement membrane.²⁾⁻⁴⁾ The alveolar epithelium has also been shown to be complete and to consist of cells which vary in thickness from about 4μ . near the nucleus to about $50\text{--}100\text{ m}\mu$. ($500\text{--}1,000\text{ \AA}$) at the periphery. This epithelium is also supported by a basement membrane.²⁾⁻⁶⁾ The alveolar air-blood barrier may, therefore, be very thin in places, e.g. epithelial layer $500\text{--}1000\text{ \AA}$, basement membrane $350\text{--}550\text{ \AA}$ and capillary endothelium $100\text{ \AA}$.

The lymphatic vessels in the lung consist of 2 connecting networks, one placed superficially in the visceral pleura and the other deeper in the lung tissue accompanying the bronchi, the pulmonary artery and the pulmonary veins. One of the characteristic features of the anatomical distribution of the pulmonary lymphatics is their absence from the walls of the atria and alveoli. Any excess interstitial fluid or extravascular protein in the region between the alveolar epithelial layer and the capillary endothelium or in the alveoli themselves must be taken up by the terminal lymphatic vessels in the region of the alveolar ducts.

Once the tissue fluid has entered the lymphatic capillaries to become lymph the flow is towards the hilar lymph nodes. This flow depends on a gradient of pulmonary pressure as well as on the direction in which the valves point. While most of the lymph in the deeper parts of the lung passes centrally towards the hilar nodes, some in the periphery of the lung may pass by communicating vessels into the pleural lymphatics which also drain into the hilar nodes after traversing the surface of the lung.

Volume of lymph flow from normal lungs

The collection of lymph from the lungs after it has passed through the hilar lymph nodes has presented many difficulties, mainly because of the small flow. Warren and Drinker⁷⁾ found that in dogs lymph from all parts of the lungs entered the right lymph duct except that from the upper section of the left lung which drained into the thoracic duct. This finding encouraged several workers to cannulate the

right lymph duct low down in the neck on the right side without opening the thoracic cavity. When flow from such a cannulated right lymph duct is based as a measure of lung lymph, it must be remembered that lymph from the serous cavities—pericardial, pleural and peritoneal—also enters this final pathway, at least in the dog and cat. What proportion of the lymph collected comes from the various regions in the normal animal is not known. The actual mean flows recorded from groups of anaesthetized animals are summarized as follows:

	<u>ml./hr.</u>	<u>ml./Kg./hr.</u>	<u>Reference</u>
Dog (18)	1.1	—	7
Dog (21)	2.3	0.1	8
Dog (5)	0.9–5.4	0.06–0.36	9
Dog (14)	0.8–35.0	0.01–1.3	10
Cat (10)	0.52	0.14	8
Rat (10)	0.1	0.3	11

It is reasonable to assume in a 20 Kg. dog a plasma flow through the lungs at rest of about 80 L./hr. Of the few ml./hr. of lymph from the vessels must, at best, be very little.

Lymph composition and protein turnover

All authors have found that the protein content of lymph from the right lymph duct is high, averaging about 3.6%. These values reflect the low capillary pressure in the pulmonary circulation rather than a high permeability, because the total leakage of protein in the lungs is small compared with most tissues, especially in relation to the intravascular circulation, which is the same in the lungs as in the rest of the body. Based on the figures obtained in anaesthetized animals the leakage of protein through the pulmonary capillaries in man would amount at the most to only 5 to 10 Gm. daily or about 5 per cent of the leakage in the tissues supplied by the systemic circulation. This reflects the low capillary pressure in the lungs as well as the fine structure of the walls of these vessels.

Lymph flow and protein leakage in acute pulmonary edema

There are many causes of acute pulmonary edema, but they act either by increasing the permeability of the capillary wall or by producing an imbalance of the pressures which control the fluid exchange across this membrane. In edema formation the basement membrane between the two cellular layers of the air-blood barrier increases in thickness, but because of their close proximity the alveoli also become filled with fluid.¹²⁾

The flow of lymph increases with acute edema formation, no matter how edema is produced. Various chemical irritants such as α -naphthyl-thiourea¹³⁾ or phosgene¹⁴⁾ have been used. In these experiments death occurred from pulmonary edema within 6 to 12 hours. The lymph flow in such cases increased manyfold and reached its highest level when large areas of the lung became solid with edema. The lymph flow in this type of acute massive edema could account for only a small amount, about 10%, of the excess tissue fluid formed. For example, in anaesthetized dogs exposed to phosgene leading to massive pulmonary edema and death in 6 to 12 hours, the leakage of protein, assessed by the protein in the

lymph before exposure and by the protein in the lymph and in the excess tissue fluid after exposure, in a group of animals of average weight 21 Kg., was as follows¹⁵⁾: Before exposure—in lymph 0.08 Gm./hr., after exposure—in lymph 0.2 Gm./hr., in excess tissue fluid 2.0 Gm./hr. These figures give the mean escape of protein over the entire period from exposure to phosgene until death.

Similar findings have been observed when the pulmonary capillary pressure has been increased by pressure on the pulmonary veins⁷⁾ by producing experimental mitral stenosis,⁹⁾ by inflating a balloon in the left atrium¹⁶⁾ or by altering the hemodynamics of the pulmonary circulation by hypoxia.^{17),18)} The lymph flow did not increase when the left atrial pressures were raised to 25 mm. Hg from the normal of -2 to +7 mm. Hg. Pressures of 30-50 mm. Hg, however, produced flows from the right lymph duct 4 to 8 times the control values. It seemed that while left atrial pressures of 25 mm. Hg or less produced no pulmonary edema, pressures greater than 30 mm. Hg caused death from pulmonary edema in 1-2 days.

In these experiments in which the atrial pressure was increased above 30 mm. Hg, the lymph became bloody in appearance due to the extravasation of red blood cells, probably by rupture of some of the blood capillaries. Such pressures of 30-50 mm. would not cause rupture of the capillaries in muscle and skin. The lung capillaries are probably less well supported than the capillaries in muscle and are in places thinner. In the liver an increase in the pressure in the hepatic sinusoids will also cause red cells to enter the hepatic lymph, probably by separation of the endothelial cells. On the other hand, edema caused by pulmonary irritants such as phosgene was not accompanied by an extravasation of red blood cells.

Lymph drainage of fluid from the alveoli

When an excess of tissue fluid is formed within the region between the alveolar and capillary walls, it soon appears in the alveoli. Although red cells and protein that have traversed the capillary wall may be rapidly removed from the tissue fluid, these substances are extremely slowly removed once they enter the alveoli.¹⁹⁾⁻²¹⁾ It seems that although transuded fluid and protein readily passes through the alveolar epithelium to enter the alveoli, the reverse process is very slow. This may be due to pressure gradients, for the alveolar fluid will only be absorbed if there is a pressure gradient from the alveoli to the deeper parts of the lungs.

These experiments show that the rich network of lymphatics normally keeps the alveolar air-blood barrier free from excess tissue fluid and protein—ideal for gaseous exchange. When protein-rich fluid enters the alveoli, however, the lymphatic removal will be very slow.

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**Blood Air Pathway with Special Reference to the Correlation
Between Structure and Function in the Pulmonary
Alveolar Basement Membrane**

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This report is concerned with the extremely interesting changes of structure and function of the pulmonary alveolar membrane for the occurrence of the pulmonary edema in the cases of mitral stenosis which were experienced in our clinic.

1) A relationship between thickening of the pulmonary alveolar basement membrane and the occurrence of pulmonary edema: In the early period of the pulmonary edema a portion of the pulmonary alveolar basement membrane with a slight degree of thickening and destruction was seen initially. An edema extends toward the intracellular space and further the interstitial space. In the results of extension of edema toward the intracellular and further interstitial space of the alveolar structure, the pulmonary intraalveolar edema comes to be formed gradually. A part of the swollen alveolar structure transudes and separates into the alveoli as a vesicle. In addition, a vesicle formed in the endothelial cell increases its size and separates in the capillary as an endothelial vesicle. However, in the instance of extreme thickening of the basement membrane (more than 2,000 Å) the formation of edema described above extends to the subendothelium at the utmost without further extension to the other structure.

2) The relationship between pulmonary alveolar basement membrane and cardiopulmonary function: There was little correlation between pulmonary basement membrane, and pulmonary arterial pressure and pulmonary wedge pressure, but in the instance more than 25 mm.Hg of pulmonary arterial pressure and less than 25 mm.Hg of pulmonary wedge pressure the mean thickness of pulmonary basement membrane is 2,600 Å and 1,800 Å respectively. However, there was positive correlation between pulmonary arteriolar resistance and the thickness of the basement membrane. In all the instance that the pulmonary edema was observed by the electronmicroscope the thickness of the basement membrane was less than 2,000 Å, pulmonary arteriolar resistance being within 200 dynes.sec.cm. In the instance of the remarkable thickening of the pulmonary basement membrane there was a decrease of D_{LCO} , D_{MCO} and V_c .