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This Week's Citation Classic®

Guyton A C & Lindsey A W. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ. Res.* 7:649-57, 1959.
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This paper demonstrated in quantitative terms that edema fluid accumulates in the otherwise normal lung only when the pulmonary capillary pressure rises to a value greater than the plasma colloid osmotic pressure and, also, that the rate of fluid accumulation increases in direct proportion to the excess pulmonary capillary pressure. [The *SCI*® indicates that this paper has been cited in over 335 publications since 1959.]

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The theoretical basis for this study was Starling's observation in 1896[1] that the proteins of plasma exert an osmotic force, called the colloid osmotic pressure, that opposes the tendency of capillary pressure to cause transudation of fluid out of the capillaries into the tissues. Most investigators, therefore, also assumed that the colloid osmotic pressure of the plasma is the principal factor that prevents leakage of fluid from the pulmonary capillaries into the alveoli. However, except for anecdotal data, little quantitative proof supporting this concept was in the literature even in the late 1950s.

When we began our experiments, we had expected to find only some semblance of a quantitative relationship demonstrating the opposing effects of the pulmonary capillary pressure and colloid osmotic pressure on net fluid movement through the pulmonary capillary wall. However, to our surprise and delight, we found an almost one-for-one relationship, showing that at all levels of left atrial pressure below about 24 mm Hg in the dog (which translates to about 25 mm Hg pulmonary capillary pressure and which is also almost exactly equal to the dog's colloid osmotic pressure), none of the animals developed pulmonary edema. However, at left atrial pressures above 24 mm Hg, the rate of development of pulmonary edema increased in direct proportion to any further increase in this pressure.

A few years later, in 1968, we also provided evidence that the fluid pressure in the interstitial spaces of the lungs is subatmospheric, about -6 to -9 mm Hg,[2,3] and that this causes continual suction of fluid through the alveolar epithelium from the alveoli into the interstitium. From that date onward, there has been continual argument whether or not this could possibly be true. This 20-year controversy has led to many excellent experiments throughout the world and has helped to characterize in highly quantitative physical terms the overall organization of fluid dynamics in the lungs. It is probably this extensive series of studies that has caused the original paper to be cited so often. We have recently reviewed the entire subject.[3]

ISI® asked whether or not this work led to any honors. Probably it did contribute to several awards that I have received, among which have been the Wiggers Award for Cardiovascular Research from the Circulation Group of the American Physiological Society, the Distinguished Physiology Lectureship Award of the American College of Chest Physicians, the American Heart Association Annual Research Achievement Award, and the Dickinson Richards Award for Cardiopulmonary Research from the Pulmonary Council of the American Heart Association.

1. **Starling E H.** On the absorption of fluids from the connective tissue spaces. *J. Physiology—London* 19:312-26, 1896. (Cited 570 times since 1955.)
2. **Meyer B J, Meyer A & Guyton A C.** Insterstitial fluid pressure. V. Negative pressure in the lungs. *Circ. Res.* 22:263-71, 1968. (Cited 105 times.)
3. **Parker J C, Guyton A C & Taylor A E.** Pulmonary transcapillary exchange and pulmonary edema. *Int. Rev. Physiol.* 18:261-316, 1979.