This essay looks at the historical significance of two APS classic papers that are freely available online:


Prior to 1960, there was a great deal of discussion in the literature over the differences between positive and negative inflation of the lungs, with particular emphasis on the pulmonary vasculature. The vasculature of the lung is unique among organs, since it is constantly subjected to rhythmic and sometimes extreme stretching. How it has adapted to these stresses was not well understood. Many investigators believed there would be a difference in the vascular response to lung inflation if the inflation occurred by lowering pleural pressure as opposed to raising airway pressure. In the first of two back-to-back papers (5), Permutt (Fig. 1) and colleagues conclusively settled this issue with a simple analysis and experiments that showed that there was no difference at all between positive and negative pressure inflation, as long as one was careful to reference airway and vascular pressures to the pleural pressure. In the companion paper (1), a clever experimental approach was used to show that the pulmonary vascular bed could be functionally separated into two parts that had opposite responses to lung inflation.

This second paper (1) was seminal in that it put forth the notion that there were two parts of the pulmonary vasculature that showed qualitatively different behavior in response to lung inflation. The companion paper (5) described the basic observations of biphasic changes in vascular volume, but it was this second paper that provided unambiguous quantification of this important phenomenon. The work gave rise to the concepts of alveolar and extra-alveolar vessels, although these terms were not applied at the time. These terms were later defined by Mead and Whittenberger (4). The paper also anticipated the concepts of pulmonary interdependence as later developed and quantified by Mead et al. (3). A simple attempt at qualitative modeling was made in the paper to describe how extra-alveolar vessels might dilate with lung inflation, but the model assumed a radial symmetry in the lung that prevented it from being more generally valid.

The paper was also novel in the approach that was taken to separate the contributions of the two compartments. This was accomplished by first studying the pressure-volume relations of the vasculature filled with dextran and then when the arterial and venous vessels were filled with kerosene. The surface tension at a kerosene-aqueous interface is sufficiently large to prevent penetration of the kerosene into the capillary space. Some 20 years later, when Jeff Smith and I were repeating this experimental setup with the goal of utilizing the newer continuum mechanics models of lung interdependence to obtain more detailed quantification, we recognized what it must have been like in those early days. For those who have not worked with kerosene in the lab, it is hard to appreciate just how it seems to have a mind of its own. The liquid seemed to go everywhere, and despite rigorous attempts to clean up, the odor would linger for months, leading in one instance to someone calling the fire department to the lab. This was just one instance of why one should not unthinkingly copy experimental procedures. After thinking about what our goal was, it occurred to us that we could more simply and more accurately accomplish the same thing by simply inflating the arteries and veins with air. This worked quite well, leading to a lengthy paper (6), but the lab still smelled of kerosene for the duration of the experiments with air.

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Fig. 1. Solbert Permutt. Courtesy of Dr. Solbert Permutt.
It is also instructive to note the fact that, as clever as the experiments in the paper by Howell et al. were, unbeknownst to the investigators, a similar series of experiments (here with latex filling of the pulmonary vessels) had already been done many years earlier (2)! This highlights the importance of doing a thorough literature search before and during new experimental and analytical work. Although this is surely easier today than it was in 1960, there is yet much work not available online that may have modern relevance.

To summarize, these two papers provided motivation for a whole series of theoretical and experimental studies that have established the structural basis of contemporary lung pathophysiology. This work has contributed to our understanding of many facets of lung function, from the widespread use of mechanical ventilation in the intensive care unit to the potential sites of vascular leakage and fluid accumulation in pulmonary edema. The results altered the vocabulary we now use to describe vascular events in the lung. Like all good papers, these papers addressed critically important issues of the day while simultaneously raising new questions requiring additional thinking, experiments, and analyses.

REFERENCES