When I was five years old, my mother took me to a movie called *Arrowsmith*, based on the great novel by Sinclair Lewis about a physician who became a medical scientist. From the time I saw that movie, I dreamed of becoming a medical scientist like Arrowsmith. The scenes in which Arrowsmith was conducting a clinical trial of a possible new therapy for bubonic plague were extremely frightening to me. From the book, which I read in my early teens, I know that the trial was being carried out on a native population of an island in the Caribbean. There were striking scenes of misery and death everywhere, and I was very sad when his wife who was a nurse died of the plague. My mother told me that I had great trouble sleeping during the next week and continually awoke with horrible nightmares. The most vivid recollection I have of the movie is of the ending. Martin Arrowsmith is obviously leaving his hospital and laboratory for good, but then, remembering that he has forgotten something, he runs back into his laboratory and picks up a strange object that my mother told me was a microscope. I had assumed that when he was leaving the laboratory and hospital, he was giving up his dangerous work, and I was glad, but it was apparent to me, even at the age of five, that his going back for the microscope meant that he was going to continue his work. My feelings must have been a mixture of grave concern for him and even greater admiration for
his bravery and dedication. When my mother explained to me what a microscope was, it took on special significance for me, because an instrument that made it possible to see invisible objects was something very powerful indeed, and I knew that when I grew up I wanted to be able to work with just such powerful instruments. Although the work might be dangerous, it would also be adventurous, and I was willing to take the risks in the same way that a policeman or fireman does.

At about the same age, I remember coloring pictures of biblical scenes in our Sunday School class. We got a gold star if we colored a picture well, a blue star if not so well, and no star if it was colored poorly. I do not think I got many gold stars because, as I later discovered, I was colorblind. Nevertheless, one day while coloring a picture of Adam and Eve in the Garden of Eden, my friend Melvin Cohen remarked that this was not the way that Adam looked but that he really looked like an ape. I did not believe him, but when we looked in his sister’s high school history textbook, we saw a strange picture of what I presume was a Neanderthal man, and the caption under the picture was “the first man.” I had absolutely no doubt that the history book was accurate, and I concluded that what I was being taught in Sunday School was false. I did not think my Sunday School teachers were intentionally lying to me, but still I knew that what they were teaching me was not true. Why I was so much more ready to accept historical over biblical information I do not know, but from then on I had more confidence in scientific models than in explanations that invoked burning bushes, parted seas, and going to heaven in a fiery chariot. I read everything I could get my hands on about science, especially medical science and evolution.

Parallel to my interests in science, I began to develop an interest in mathematics. I was no more competent in arithmetic or mathematics than any of my classmates, but I was more intensely interested and puzzled by a number of strange mysteries. Marvin Udelson, a friend of mine who was a few years ahead of me in school, kept showing me strange things that he was learning that bewildered me. He must have enjoyed my failure to understand what he clearly grasped. Did I know that there could be numbers that were less than nothing? All you had to do was put a minus sign in front of a regular number. How could there be something less than nothing? Did I know that you could divide a smaller number by a larger number? How could you divide a smaller number by a larger number? Did I know that if you didn’t know what the answer was, you could substitute an x for the answer and then by some magical process come out with the answer? I began to look at mathematical books in the library that were filled with the most beautiful and mysterious symbols. I then learned that these symbols were the language of science. I knew that if I could learn to use such symbols along with instruments like microscopes, I could make important discoveries and probably have lots of fun at the same time. That is what I wanted to do when I grew up. In essence, it is what I have tried to do with my life, but I encountered some major detours along the way.

After a year of premedicine at the University of Alabama, I was drafted into the army in 1943 at 18 years of age. The army sent me to school in uniform for both premedicine and one year of medical school before the war was over in 1945. In 1949, after receiving my M.D. degree, I took a year’s medical internship at the University of Chicago. I loved the exhilarating intensity of housestaff training, but clinical medicine was not what I had pictured for myself. I wanted to be working at “the cutting edge of science.” So instead of continuing with my housestaff training, I went to work in the Department of Anatomy at the University of Chicago on the properties of the intercellular matrix, then
called the ground substance, in the laboratory of Isadore Gersh. Even by today’s standards, I was working at least near the cutting edge.

The next two years were pure misery. It was not that I had no moments of great joy in the work—on the contrary, I could sometimes feel pure ecstasy, but that was part of the problem. I could not control the rapid oscillations between feeling that my work was on the verge of being outstanding and that all of my endeavors were completely worthless, that I was second rate, and that medical science was for someone else, not me. I probably could not have chosen a field for which I was more unsuited. Most of my time was spent describing microscopic sections. Besides my color blindness, something more fundamental was in my way than having chosen the wrong field. I was not mature enough to know how to cope with the problems of working in science as a professional and doing what had to be done without inspiration. For me it was ecstasy or nothing. I began spending more and more of my time in the university commons playing chess and bridge and less time in the laboratory.

I also became heavily involved in what were then considered left-wing political activities right at the time the whole country was responding with mass hysteria to the dangers of communism, “the great Red scare.” My rather mild political activities, such as supporting friendship with the Soviet Union and China and outlawing the atom bomb, put me into direct conflict with Joe McCarthy and his ilk.

During this awful period of my life, when the future looked so dismal, I met Loretta, my wife for more than 40 years. I was amazed then, and am still amazed today, that she had no concerns about a future with me. We got married in January of 1952.

In July of that year I gave up all notions of ever doing medical science and went back to my house staff training at the University of Chicago, but, by January of 1953, because of the doctor’s draft, because we were involved in a shooting war with Korea, because I had my medical education at government expense during the Second World War, and because I refused to inform on my friends and associates in the political movements in which I had been involved, I was drafted into the army as a private. After finishing 12 weeks of basic training for enlisted men at Camp Pickett in Virginia as a medical corpsman, I was sent to Fitzsimmons Army Hospital in Denver at the rank of private.

Fitzsimmons Army Hospital was one of the outstanding institutions in the entire world in the field of tuberculosis, and I was lucky to have been sent there, even as an enlisted man. After a while, when the authorities saw that I was not interested in subverting the army, they assigned me as an assistant to William Harris, a remarkable physician, trained by Amberson, who later became the chief of the unit that Amberson had founded at Bellevue. My life was changed forever. He was an inspiring teacher. After a few months of exposure to him, I never wanted to do anything except pulmonary medicine, and I would have been perfectly happy to spend the rest of my career in the field of tuberculosis. Bill wanted to set up a nontuberculous chest service at Fitzsimmons, and he apparently persuaded the establishment at Fitzsimmons that I was capable of running the large tuberculosis ward of which he had been in charge. This I was allowed to do as a private with the help of a nurse who was a major. Bill went on to create the first nontuberculous chest unit at the hospital. During this same period of time, I also received outstanding support from William Stead, now the director of the tuberculosis programs of the Arkansas Department of Health, who taught me how to use pulmonary function tests in the clinical evaluation of patients with respiratory impairment.

I now was very happy. I rejected the notion of becoming a medical scientist
like Martin Arrowsmith; being a good pulmonary clinician was more than enough to satisfy my now considerably modified ambitions. I still had a few obstacles to overcome, however. The principal one was that McCarthy accused the army of employing communists. This was the basis of the Army-McCarthy Hearings at that time. The army responded in a most courageous and forthright manner—after drafting me, they gave me an undesirable discharge.* This was in April 1954, and I now had a serious problem. If I was going to be a pulmonary physician, I needed more house staff training and more clinical training in pulmonary medicine. It should not be surprising that there were essentially no jobs whatsoever available to me when I informed the selection committees of my dubious relations with the United States Army, which I believed I had to do because I knew my story would come out later anyway. I had outstanding letters of support from Bill Harris, Bill Stead, and even the general in charge of Fitzsimmons Army Hospital, but no house staff positions or fellowships were offered. Late in June of 1954, Robert Bloch, a former professor of medicine at the University of Chicago whom I had known and who was then head of the Pulmonary Division of Montefiore Hospital in New York, telegraphed me that he would like me to be his chief resident, but he could not offer me the position unless I was willing to come to New York at my expense and be interviewed by the board of trustees of the hospital. I went to New York, the board of trustees approved of me, and I finished my formal house staff training there.

My 2 years at Montefiore Hospital were very happy ones. The first year I supervised the interns and residents who rotated through the Pulmonary Division as part of their required house staff training in medicine. The following year I became the chief resident of the Department of Medicine. I was asked to consider a part-time or full-time clinical position in the Pulmonary Division following my training, and it was my firm intention to remain in New York in clinical pulmonary disease.

While at Montefiore Hospital I became interested in several scientific questions that grew out of my clinical activities. What controlled the size of a tuberculous cavity? Did pneumothorax decrease the size of the cavity because the pressure within the cavity decreased relative to the pressure at the pleural surface of the lobe, or did the cavity decrease in size because the surrounding lung tissue was under less elastic tension? I was fascinated with the controversies I read about in the medical literature. Some favored pressure, others tension, but it seemed to me that elastic tension was more important. A hole in a rubber membrane gets smaller when it is not stretched even though there is no change in pressure. I could not have realized at the time that the relationship between the size of the cavity as a function of distending pressure versus elastic tension of the surrounding tissue would become a major focus of my later scientific work: mechanical interdependence of the elements of the lungs.

As I read more about how the partial pressures of oxygen and carbon dioxide in the arterial blood were dependent on the state of pulmonary function, it seemed to me that the gas pressures of the venous blood would reflect the state of systemic function. I started spending some time in the cardiac catheterization laboratory and even carried out a few unfocused projects on oxygen saturation in venous blood.

My intense interest in scientific ques-

*In keeping with the increasing recognition of the perniciousness of McCarthyism, the Undesirable Discharge I received on April 29, 1954, was changed to a General (under honorable conditions) Discharge on November 12, 1957, and to an Honorable Discharge on April 14, 1958. By the end of 1958, I had received back pay as a medical officer with the rank of captain.
tions and my enthusiastic communication of these ideas in numerous conversations with my colleagues at Montefiore led a number of my advisors to conclude that I showed considerable promise for creative scientific work in medicine. They suggested that I would do well to consider training with one of the groups that was applying modern concepts of respiratory physiology and pulmonary function testing to the newly developing field of pulmonary medicine.

I would have liked to believe that my advisors were correct, but I felt that my knowledge and enthusiasm for science that I had since a young child were overrated as predictors of success. I thought I had already had the opportunity to become a medical scientist, and I had failed. I did not want to fail again. My advisors, persuaded me, however, that one or two years of research training in respiratory physiology would make me a better clinician and teacher if I chose to return to Montefiore. Loretta also encouraged me to try one more time to see if I might have a future as a medical scientist.

In early 1956, I visited several groups that were at the forefront of modern respiratory physiology and pulmonary medicine. I decided to apply for a fellowship with Richard L. Riley’s group at Johns Hopkins because Riley had developed the only method of measuring blood O₂ and CO₂ tensions then in use and also had been involved with the development of cardiac catheterization through his work with Courand and Richards. I thought work in his laboratory would provide me an opportunity to test my ideas about the significance of venous gas tensions. Riley offered me a fellowship starting in July 1956 with support from the National Foundation for Infantile Paralysis.

What a magnificent place was Riley’s laboratory! There were not yet clinical subspecialty divisions of the Department of Medicine at Hopkins. Riley’s laboratory was part of the Physiological Division of the Department of Medicine, which contained the pulmonary function laboratories and the heart station of the Johns Hopkins Hospital. Only two members of the faculty were at Riley’s laboratory: Riley himself and Richard Shepard. Riley’s laboratory was filled with fellows from all over the world; the interaction between the fellows with each other and with Riley and Shepard was unforgettably exciting and productive. A few large projects in clinical investigation were being pushed forward by Shepard and Riley with the participation of the fellows. The fellows also were responsible for consulting and performing pulmonary function studies on patients from the Johns Hopkins Hospital. Most of their activities, however, arose spontaneously through their contacts with each other.

After I had been in the laboratory for a few months, Harry Martin, a fellow in his second year of training, asked me if I would be interested in working with him on measuring the static pressure-volume relations of adult subjects to see if the lungs lost elastic recoil with age. I accepted the invitation. I had first met Harry Martin at Fitzsimmons Army Hospital, and I had great affection for him because he had never let the difference between his rank of captain and my rank of private interfere with warm and friendly relations between us and our families.

We assumed the pressure in a balloon in the esophagus would approximate the pressure on the pleural surface of the lungs, and the difference between airway and pleural pressure when there was no air flow would be a measure of the elastic recoil pressure of the lungs. We measured the pressure-volume relations throughout the entire vital capacity range and measured residual volume by helium dilution. We thought the shape of the curves and the magnitude of hysteresis represented a fundamental property of the lungs. In a sense, this is true, but it was not as simple as we thought.
J. B. L. (Jack) Howell, another fellow in the department, and I were assigned the task of giving demonstrations of pulmonary function tests to Hopkins medical students in the spring of 1957. Howell was an expert in pulmonary mechanics. In addition to his medical degree, he had received a Ph.D. in physiology from studies on the mechanical properties of the lungs of human subjects while working in the laboratory of Sampson Wright at the Middlesex Hospital in London. We both thought it would be a great idea to show the medical students how to measure the elastic properties of the lungs, as Martin and I had just done and Howell had done for his Ph.D. degree. We thought it would be much simpler and much more reproducible to carry out these measurements in open chest anesthetized dogs, and we would not have to do a hard sell to the medical students to get them to swallow balloons. But we never made the demonstration to the students because we could never get a single reproducible curve. We got markedly different recoil pressures at the same lung volume depending on the inflation history to achieve the volume (Fig. 1).

A lung was degassed in vacuo, inflated to 30 cm H₂O, then deflated to 0 cm H₂O. An inflation-deflation procedure was then carried out as shown in Figure 1. The pressure was changed by 2 cm water steps, and the volume was measured at 1 min following the change. In 11 of 13 dogs, we produced marked degrees of trapping. It was clear that the trapping was due to airway closure occurring at progressively higher airway pressures, as indicated by the deflation inflections moving progressively to the right and the progressively higher opening pressures on inflation.

John Clements, who was then working at the Army Chemical Center, frequently visited Riley’s department, just at the time he was forming his ideas on the significance of surfactant. We assumed the overinflated state that was produced by the slow inflation-deflation cycles was a function of altered surface tension, because the whole cycle could be repeated if the lung was degassed in vacuo and a new surface formed. Further, the saline pressure-volume curve (which John Clements showed us how to carry out) was normal.

I presented these findings at the fall meetings of the Physiological Society in Iowa in 1957. It was my first presentation of a paper at a scientific society. Speaking for both Jack Howell and myself here is what I said:

The fact that repeated inflation-deflation cycles lead to a condition where bronchi are occluded with positive pressure across the lung is somewhat surprising. Certainly, it would appear unlikely that the properties of the bronchial wall have been altered in such a manner to cause them to close at higher pressures across the lung. One possibility is that the critical closing pressure across the bronchi remains the same, but the interstitial pressure surrounding the bronchi has increased above the ambient pressure of the lung.*

What Howell and I were getting at was a model of the lung that was essentially a system of small bubbles within an elastic tissue matrix. We thought that the slow and repeated inflation-deflations led to an accumulation of so much of John Clements’s surfactant that the bubbles had virtually no recoil pressure on deflation. Nevertheless, the recoil of the stretched tissue elements produced a high interstitial pressure that squeezed on the bronchi.

*In retrospect, the relationship between critical closure and surrounding pressure, which has dominated my thinking for 35 years, was implicitly considered in my first presentation of a paper at a scientific society.
Figure 1. The lung from a dog was degassed in vacuo and placed in a plethysmograph with the trachea connected to an external spirometer. The lobe was inflated by lowering the pressure within the plethysmograph. It was first inflated to a transpulmonary pressure of 30 cm H$_2$O, then deflated to zero transpulmonary pressure. Then a series of five inflation-deflation cycles were carried out. These relations are shown on the left. Pressure is equal to atmospheric minus plethysmographic pressure (transpulmonary pressure), and the volume of the lobe is determined from the spirometer. The entire process was repeated for the curves shown on the right, except that the fourth inflation-deflation cycle was omitted. (From presentation at fall meeting of the American Physiological Society in 1957.)

and caused them to close at high lung volumes. If the positive interstitial pressure were squeezing on the airways, it must also be squeezing on blood vessels, and if we could attach a manometer to the blood vessels under conditions where their volume was held constant, we could use the blood vessels like an esophageal balloon—but a balloon within the interstitium of the lung rather than within the pleural cavity. Donald Proctor, who had worked with Harry Martin on the pressure-volume relations of excised bronchi, joined us for these experiments.

The method we used is shown in Figure 2. We inflated the lobes by lowering the pressure within the box: negative-pressure inflation. At the time we carried out this work, there was still widespread belief that positive and negative pressure inflation had different effects on pulmonary blood vessels. We showed that the effects were identical as long as the vascular and airway pressures had the same relation to each other as is shown in the figure.

The vein and artery of a lobe of a dog's lobe were connected to a common tube, which in turn was connected to one end of a water-filled manometer. Between the vessels and manometer was a small air-filled syringe, which created an air space between the vessel and manometer. The vascular pressure at a transpulmonary pressure of zero was set by controlling the level of the liquid meniscus in the vertical tube relative to the top of the lobe. As the lobe was inflated, the meniscus was kept
at the same level by pulling or pushing the barrel of the syringe and recording the pressure on the manometer necessary to keep the level fixed. We believed that most people would think that the pressure in the manometer would not change because they would assume that the interstitial pressure would remain constant and equal to pleural pressure. We were hoping to see a rise in the pressure around the vessels due to an increase in the interstitial pressure, and because of our nearly complete ignorance of the pulmonary circulation, we believed that this would be a big discovery. And that is exactly what happened—in the first experiment.

I remember vividly how we called in other fellows to share with us these momentous findings. The same results happened on several more occasions, but then one day, when we grabbed hold of some unsuspecting (and probably bored) colleague to show him truth, exactly the opposite happened: with lung inflation, the pressure fell. This was a jarring emotional experience consisting of a mixture of some surprise, some disappointment, and utter confusion.

After a while we learned how to make the pressure go either way or hardly change at all by setting the initial level of the meniscus a little above, a little below, or right at the top of the lobe (Fig. 3). With the initial level just a few centimeters above the top of the lobe, we had to apply more than 20 cm H$_2$O positive pressure from the syringe, and with the initial level a few centimeters below the top of the lobe, we had to apply more than 20 cm H$_2$O negative pressure. These results established that lung inflation could either squeeze or pull on the pulmonary vessels. Although we could control the direction of the change, we did not know why a small change in the initial pressure could have such a profound difference on the response.

Now other people became interested in what was going on. Dick Shepard referred to this as the "flower pot" experiment because that is what he was reminded of when he looked at the symmetrical arrangement of the curves of Figure 3. Jack Howell and I would take the graphs of the experimental data to Dick Riley's house to discuss them with him. He was staying at home taking chemotherapy for a mild flare-up of his tuberculosis. It was Riley who figured out what was going on. He said that the shape of a lobe during inflation changed from something like a thin slice of pie to a thick slice with the point of the slice analogous to the hilum. He believed that during inflation the wid-
Figure 3. Vascular pressure relative to the pressure at the pleural surface of a dog’s lobe required to maintain a constant vascular volume, plotted against alveolar pressure relative to pleural pressure. The hydrostatic level is the top of the lobe. (From reference 23.)

Figure 4. As the pressure in the balloon within the Krogh spirometer was inflated with positive pressure, the fluid level within the spirometer rose, indicating that the pressure on the outer surface of the balloon had become negative relative to atmospheric pressure at the same time that the pressure within the balloon became positive relative to atmospheric pressure. Similarly, the pressure within the space confined by three cylindrical balloons became increasingly negative relative to atmospheric pressure as the pressure within the balloons became increasingly positive. (From reference 23.)

The lengthening of the lobe would exert a traction on the larger blood vessels, while the smaller peripheral vessels would be compressed by the increasing pressure in the alveolar spaces. He said that we should be able to model this with a Krogh spirometer by having struts pull on an elastic tube traversing the spirometer from its axis and terminating inside of a balloon within the body of the spirometer itself. We would see that the conducting tube was widened by the attached struts while at the same time that portion of the tube within the balloon would be compressed. We made a transparent Krogh spirometer, but we never had to put the struts in place, for when a balloon was inflated inside the spirometer, we could see the fluid level rise (Figure 4)! This seemed then and even now both beautiful and amazing, but the explanation is simple. The space around the balloon was essentially constant, and the enlargement of the spirometer produced by
the positive pressure in the balloon produced a negative pressure of the surrounding air. In an analogous way, we reasoned that the constancy of the interstitial volume of the lung tissue required a negative pressure as the alveoli enlarged with positive pressure. We also showed that if we put three cylindrical balloons inside a third balloon, simultaneous inflation of the three balloons caused the pressure between the balloons to become negative.

We now reversed our initial concept of interstitial pressure: rather than being positive, we inferred that it is usually negative and becomes increasingly so with lung inflation. Only years later did Ed Faridy and I figure out what caused the closure of the airways in the overinflated state.\(^2\)

This is how we explained the flower pot experiment: inflation always pulled on the larger vessels and squeezed on the smaller ones. At low initial pressure, there was not much liquid in the small vessels, so inflation was dominated by what happened to the larger ones. At high initial pressure, more liquid was pushed out of the small vessels than could be accommodated by the expanding larger ones. At intermediate pressures, the opposing effects on simultaneously compressed and expanded vessels was balanced. We became confident in the soundness of this concept when we examined the effect of lung inflation on vascular volume at constant vascular pressure (Fig. 5).\(^{19}\) The top panel shows the effect of a change in vascular volume on the abscissa against lung volume on the ordinate. The lower panel shows the change in vascular volume against transpulmonary pressure. Each panel shows three curves for three different vascular pressures. The vascular pressure was held constant by connecting the vein and artery to a horizontal burette held at a fixed level relative to the top of the lobe. On the left, the burette was 4 cm above the top of the lobe; on the right, 4 cm below the top of the lobe; and for the middle curve, the burette was at the top of the lobe.

Consider first the left-hand curves. As the lung was inflated, more liquid was squeezed from the small vessels than could be accommodated by the larger ones, and liquid moved from the vessels to the burettes. With a sufficiently high level of inflation, there was no more liquid to be squeezed out, so only the expansion of the larger vessels was apparent, and liquid moved from the burettes into the pulmonary vessels. For the middle curve, qualitatively the pattern was the same, but
there was less liquid in the compressed vessels so the expansion of the larger vessels became apparent at a lower state of inflation. On the right, with still less liquid in the compressed vessels, the expansion of the larger vessels was apparent throughout the range of inflation.

These curves were fairly convincing, but there was only a limited range of inflation to demonstrate the expansion when the vascular pressure was high. We wanted to study the larger vessels independently and show that they expanded throughout inflation regardless of the vascular pressure. To do this we needed a way to block the smaller vessels from the larger. It was again through sheer ignorance that we were led to a method that worked. For reasons not at all apparent to me now, we thought that it would be better to do experiments with the blood vessels containing dextran solution rather than blood. We later showed that the experiments worked perfectly well with blood in the vessels, so I do not know why we felt compelled to remove it and replace it with something else. Nevertheless, the experiments were always preceded by a prolonged washout of the blood with the dextran solution, and often the lungs became somewhat edematous. We purchased some kerosene from a small nearby store, but we found that we could not get it to pass through the pulmonary vessels even with very high pressures, presumably because of interfacial surface tension. After many unsuccessful attempts to establish a block with plastic microspheres or lycopodium spores between the small and the large blood vessels, it occurred to us that the kerosene, still sitting around the lab, might provide just the type of block we needed for the same reason that we could not perfuse the lung with it. We emptied the small pulmonary vessels by high inflation pressure and then replaced the dextran with kerosene, which filled only the larger vessels while the small vessels remained unfilled. Kerosene always moved into the pulmonary vessels with inflation regardless of whether the burettes were above or below the top of the lobe.

We now had a method of dividing the pulmonary vessels into two compartments, and we could show that the two compartments responded in an exactly opposite fashion to lung inflation. The pressure-volume relations of the vascular bed when the blood vessels were filled with kerosene were those of the large vessels, which were expanded by lung inflation. The pressure-volume characteristics of the small blood vessels, which were compressed with lung inflation, could be studied by subtracting the kerosene pressure-volume curve from the dextran pressure-volume curve (Fig. 6). We called the two compartments the expanded and compressed compartments. Jere Mead wrote a review article for the Handbook of Physiology on lung inflation and hemodynamics in 1964 and designated the vessels that composed our two compartments alveolar and extra-alveolar vessels, much more suitable words than what we chose, and these words have stuck.

We later found that Charles Clifford Macklin had used a latex solution in much the same way that we had used kerosene. He had understood the significance of our major findings in 1946, but his work had been given almost no consideration in the literature on pulmonary circulation. Macklin not only anticipated the compartmentalization of the pulmonary blood vessels, but he also contributed to our

*I think I know where Jack might have gotten the idea. Eleven pages after the abstract of reference 18 in The Physiologist of 1957 is the following abstract: Effect of perfusion pressure on the “circulating volume” of the isolated canine kidney perfused with a kerosene–mineral oil mixture by Irving Green et al.*
knowledge of pulmonary surface-active material. This work too had been unappreciated. In 1976, Staub, Clements, Proctor, and I held a symposium of the work of Charles Clifford Macklin that unfortunately had not been appreciated during his life.24 He had died in 1959.

Up to this point, we had studied the pulmonary vessels only under static conditions. We then became interested in how lung inflation affected flow through the pulmonary vessels. If the small pulmonary vessels did not resist collapse and were functionally surrounded by the gas pressure in the alveoli, we predicted that inflating a lobe at constant vascular pressure would cause a decrease in the flow because of the greater effect of compression of small vessels than expansion of the larger ones and complete cessation of flow when the alveolar pressure equaled the pulmonary arterial pressure measured relative to the most dependent portion of the lobe. Such an experiment is shown in Figure 7.23

The lobe was perfused from an arterial reservoir 12 cm above the most dependent portion of the lobe to a venous reservoir at a lower level. We predicted that the flow would cease when the alveolar pressure was raised to 12 cm H₂O. This is where the arrow is placed. It was apparent that there was virtual cessation of the flow at that point, but a small amount of flow still remained until the alveolar pressure was raised to a considerably higher level. We suggested that this remaining flow might be occurring through vessels at the junctions of the alveolar septa (corner vessels)22 because they would be protected against the full transmission of alveolar pressure due to the highly curved surfaces. But this small amount of flow did not keep us from feeling rather certain that most of the vessels of the compressed compartment, or alveolar vessels, as they were later called, were surrounded by pressure equal to alveolar pressure.4

In 1958, I went to the National Jewish Hospital in Denver as the director of both the pulmonary function and cardiac catheterization laboratories. Jack Howell went back to England, where he later became
chairman of medicine and then dean of the medical school at Southampton. He has been a recent president of the British Medical Society. I now began working with Baruch Bromberger-Barnea and Harry Bane in a fine animal research facility (Fig. 8). We wanted to know how lung inflation affected the pulmonary circulation during life. We hoped to show that the highly artificial experiments on excised lobes with the blood replaced by dextran or kerosene had some relevance.

We measured pulmonary blood flow by the Fick principle using steady-state

Figure 8a. Solbert Permutt (left) and Baruch Bromberger-Barnea working at the National Jewish Hospital in Denver in 1958.

Figure 8b. Harry Bane, André Cournand, and John West. Aspen conference, 1962.

Figure 8c. J. B. L. Howell, Sol Permutt, and Dick Riley. Aspen conference, 1962.

Figure 8d. Dick Riley, his wife Polly, Sol Permutt, and Richard Shephard. Federation meeting, Philadelphia, 1958.
oxygen consumption and the difference in arterial oxygen content between the systemic and pulmonary arteries, and we attempted to systematically study how lung inflation affected pulmonary vascular resistance in anesthetized dogs. We made measurements with the dogs breathing either spontaneously or with intermittent positive pressure ventilation at various levels of end-expiratory pressure. We devised methods of increasing transpulmonary pressure at constant pleural pressure or increasing pleural pressure at constant transpulmonary pressure. We could change cardiac output by adding or withdrawing blood. We made 90 measurements of pulmonary vascular resistance in 14 dogs at various levels of transpulmonary pressure, pleural pressure, and cardiac output. I presented these findings at the fall meetings of the American Physiological Society in 1960\textsuperscript{13}:

Where lung size was increased, pulmonary vascular resistance showed an inverse relationship to left atrial minus alveolar pressure. . . . To us this suggests that the site of the increase in vascular resistance associated with increasing transpulmonary pressure is located in small vessels whose intraluminal pressure is approximated by left atrial pressure and whose extraluminal pressure is approximated by alveolar pressure.

We considered the pulmonary circulation to have two resistances in series (Fig. 9). $R_1$ is the resistance of the arterial extra-alveolar vessels. $R_2$ is the resistance of the alveolar vessels. We assumed that the intraluminal pressure of the alveolar vessels was equal to left atrial pressure, and the pressure on the outer surface of the alveolar vessels was equal to the alveolar pressure. We believed that these two pressures algebraically summed to create some sort of graded constriction of the alveolar vessels to account for the negative correlation between pulmonary vascular

\begin{figure}
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\caption{Figure 9. This is from the original slide shown at the fall meetings of the American Physiological Society in 1960 (reference 13). I think the model is still useful today.}
\end{figure}
resistance and left atrial minus alveolar pressure.

One afternoon between the fall meeting in 1960 and the spring meeting in 1961 of the American Physiological Society, it suddenly dawned on me that this was not how the system acted. I became convinced that our results were not explained by graded constrictions but, rather, by the effect of alveolar pressure on the back pressure to flow. When the left atrial pressure was greater than the alveolar pressure, it was the back pressure to flow through the pulmonary vessels, but when the alveolar pressure was greater than the left atrial pressure, the alveolar pressure was the back pressure to flow. It suddenly seemed inescapable that when alveolar pressure was higher than left atrial pressure, the pressure at the downstream end of the alveolar vessels could be neither higher nor lower than the alveolar pressure and therefore must be equal to the alveolar pressure.

I suddenly realized that afternoon that in effect a "waterfall" exists between the collapsible alveolar vessels and the left atrium, and raising or lowering the left atrial pressure when it was lower than alveolar pressure has no more influence on flow through the system than raising or lowering a bathtub affects the water coming out of a shower. That same afternoon, Baruch Bromberger, Harry Bane, and I started replotting the data we had presented at the fall meetings. If the waterfall idea were correct, there would be a single pressure-flow curve for each of the 14 dogs if the appropriate back pressure were used. That is essentially what we found, and we presented our ideas of the vascular waterfall at the spring meeting of the American Physiological Society in 1961.14

We next tried to see if we could demonstrate an absence of the effect of a change in left atrial pressure when it was below alveolar pressure. We cannulated the pulmonary vein to the left lower lobe in open chest, anesthetized dogs and recorded on an x-y oscilloscope instantaneous changes in flow from the pulmonary vein as the pressure in the vein was slowly changed. The flow through the rest of the lungs was left undisturbed. Pulmonary arterial pressure was held constant at any desired level by either varying venous return or connecting a reservoir to the main pulmonary artery.

An example of the effect of varying pulmonary venous pressure on the flow through a pulmonary lobe at constant pulmonary arterial pressure is shown in Figure 10.15 The lower curve was obtained first as venous pressure was slowly raised. Flow ceased when pulmonary venous pressure equaled pulmonary arterial pressure. The upper curve was then obtained as pulmonary venous pressure was slowly lowered. The dashed vertical curve is at the level of the alveolar pressure, which was held constant.

We were satisfied that the predictions of the waterfall model were supported, but we noted these exceptions: (1) hysteresis was present, (2) the point of maximum flow occurred at a higher level than alveolar pressure, and (3) as venous pressure was lowered below the level of alveolar pressure there was a significant decrease in flow.*

The most impressive support for the waterfall model came from the effect of a

*Several years ago, Fung and Yen attempted to account for the hysteresis and the decrease in flow as venous pressure was lowered beyond the level of the maximum flow. They used a distributive model that had the added feature of recruitment and derecruitment of alveolar vessels. (Fung, Y. C., Yen, R. T. New theory of pulmonary blood flow in zone 2 condition. J. Appl. Physiol. 60: 138–150, 1986). The reason the maximal flow occurred at a level higher than alveolar pressure suggested to us that tone in alveolar vessels could be additive to the effect of alveolar pressure. This certainly appears to be so in hypoxic pulmonary vasoconstriction in the pig (see reference 19).
The relationship between flow (\(Q\)) and pulmonary venous pressure (PVP) at constant pulmonary arterial pressure in the left lower lobe of an open chest dog. The broken vertical line represents the level where alveolar pressure in the lobe was held constant. The lower curve was obtained first, as venous pressure was raised; the upper curve was then obtained, as venous pressure was lowered. (From reference 15.)

An increase in alveolar pressure had little effect on the shape of the curves (Fig. 11). An increase in alveolar pressure caused a slight decrease in the slope of the pressure-flow curve at pulmonary venous pressures close to the level of the pulmonary arterial pressure, but the major effect was merely a displacement of the curves in the direction of the change in alveolar pressure, and the shift was essentially equal to the change in alveolar pressure.

When Jack Howell and I were still working together at Hopkins, he told me how Moran Campbell had put a condom in a cigar box, which he pressurized to create a special type of load against which human subjects breathed, now called a threshold load. Jack and I always referred to such a system as a Campbell resistor. Shortly before my presentation of the waterfall model at the spring meetings of the American Physiological Society in 1961, I was explaining to John Clements how the pressure-flow relations of a Campbell resistor were like those of a waterfall. He was shocked at my ignorance and informed me that such a system was called a Starling resistor, which Starling had used in his heart-lung preparations. My career has relied on Starling resistors, both conceptually and experimentally ever since.*

In June of 1962, at the Fifth Annual

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*As a major focus of my work I have used the Starling resistor model and the waterfall analogy to analyze the effects of smooth muscle tone on blood vessels and airways. This concept has been applied by many of my colleagues and other workers to analyze the effects of bronchomotor tone and the pressure-flow relations of the coronary, cerebral, renal, and striated muscle circulations. See S. Permutt, and R. L. Riley, Hemodynamics of collapsible vessels with tone: the vascular waterfall. *J. Appl. Physiol.* 18: 924–932, 1963.*
Aspen Conference, I presented a model of the pulmonary circulation that consisted of nothing more than one Starling resistor stacked on top of another. I was satisfied that such a model could very nicely, or at least to my satisfaction, explain the data from every study of the effect of lung inflation on the pulmonary circulation of which I was then aware. This model has been used extensively by a number of investigators to simplify what might otherwise appear complicated. The most notable success was by John West and his colleagues, who explained the effect of gravity on the distribution of pulmonary blood flow. The opposite effects of lung inflation on the alveolar versus extraalveolar vessels has been used to provide understanding of the effect of lung inflation on fluid balance and the vasoconstrictor effects of hypoxia. The concepts have also been used to explain how vasoactive agents and pulmonary edema influence hemodynamics. To me, the greatest success of the model is that it has provided a framework that allows a systematic approach to the mechanics of the pulmonary circulation. At the end of the published paper from the Aspen Conference of 1962 this is what we said:

... we feel that the model we have presented allows the integration of a number of hitherto isolated facts concerning the pulmonary circulation into a coherent picture. To the extent that the model fails to give a complete explanation of experimental findings, it is, perhaps, most useful, for one must think in terms of new experiments and improved models.

Anyone who knows me at all must realize that I was not being sincere. I have tenaciously hung on to every detail of the model long after it was decent to do so. Recent studies suggest that the major effects of gravity cannot be explained by the model we proposed. There is evidence from studies of Dawson, Linehan, and coworkers that changes in pulmonary venous pressure continue to have some influence on alveolar vessels that would not be predicted by the waterfall model. Linehan and Dawson explain such effects by invoking a variable resistance model rather than a waterfall or Starling resistor model. Of course, I had completely rejected the variable resistance model with the sudden revelation of the waterfall in 1961!

I must admit that I get a little pleasure when people criticize the model. This means that it is still very useful. When you are young, you are always worried about what people are saying about you, but when you grow old, you realize that they are usually saying absolutely nothing. Criticism is a lot better than nothing!

As I look over my work on the pulmonary circulation during the last 35 years, it is fascinating to see the constructive role of complete ignorance at the start. Jack Howell, Don Proctor, and I would have never carried out the flower pot experiments if we had had the slightest awareness of the literature on pulmonary circulation at the time. There had been heated controversies on the effect of inflation of the lungs on the pulmonary circulation for more than 200 years prior to the time of our initial work. Interestingly, nearly all of the controversies were not related to what the experimental results were but, rather, to the interpretation of these results. Initially our interpretation of our experimental results was met with great resistance and skepticism. It is still somewhat painful to read the critical and even harsh comments made of our work by members of the pulmonary circulation establishment in the discussion that followed two major presentations. At the time we carried out our initial experiments, anyone who had made even a cursory review of the literature on pulmonary circulation would have realized that when the lung
was inflated under conditions where the pressure in the alveoli rose relative to the vascular pressure, so-called positive-pressure inflation, the pulmonary vessels would be squeezed. Anyone who knew anything about the literature on the pulmonary circulation would have been nearly certain that one would have to apply a pressure to the pulmonary vessels to keep their volume constant when the lung was inflated, something we thought would be a great discovery. The level of certainty was so great that no one had ever carried out studies on the effect of inflation on vascular pressure at constant vascular volume. Our ignorance gave us the opportunity of making a novel observation on the pulmonary circulation, that is, positive-pressure inflation causes a decrease in the vascular pressure at constant vascular volume when the vascular volume is low, in spite of the predictable increase when the volume is high.

These experiments forced us to make a comprehensive analysis of the effects of lung inflation on the pulmonary vascular bed that was independent of the special conditions of the inflation. Nearly all of my studies on the pulmonary circulation since that time have focused on improving the comprehensive analysis. The apparently striking differences between the hemodynamic effects of positive- and negative-pressure inflation still give rise to mistaken inferences concerning the effects of inflation on the pulmonary blood vessels. No one has any difficulty understanding how the alveolar vessels are squeezed under conditions of positive-pressure inflation, because one sees a rise in pulmonary arterial pressure and a decrease in pulmonary arterial flow. It is still not so easy to see how a spontaneous increase in lung volume causes the alveolar vessels to be squeezed where the inflation is accompanied by a decrease in pulmonary arterial pressure and an increase in pulmonary arterial flow.\(^{19}\)

What has happened to me in the more than 35 years that I have been working in this field is that I am no longer ignorant. Some might even consider me a sort of sage. My sagacity compels me to fight the ignorant ideas of my younger colleagues in the same way the sages of my young days fought me. But I wish I were ignorant again. I wish I could come up with some idea that no one with wisdom and knowledge would ever consider. Ignorance is indeed bliss!

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**References**


10. Martin, H. B., and D. S. Proctor. Pressure-


