expeditions. Sometimes the best we can do for imaginative investigators is to leave them alone so that one thing can lead to another. Making it possible for physician-scientists to examine the mysteries of human physiology and disease in their own style may lead them into blind alleys, but sometimes to breathtaking new vistas. I believe this is as true now as it was in 1956, and I thank Vince Dole and the JCI for reminding me.

Nearly fifty years ago, Arthur B. DuBois, Julius H. Comroe Jr., and their colleagues published two papers on the use of body plethysmography to measure lung volume and airway resistance. These two articles in the JCI are almost the most-cited doublet in the Journal’s entire archive. Remarkably, the methods described then are still in use today in clinical pulmonary function laboratories. Though body plethysmography had been used before, there were serious technical problems; it was extraordinary that DuBois managed to solve most of these in one week. Times have changed and molecular medicine now dominates the JCI, but these articles remind us that biomedical research goes beyond the molecular.

Congratulations to the JCI on the occasion of its 80th birthday. Happily the editors have used the occasion to highlight two papers by Arthur B. DuBois, Julius H. Comroe Jr., and their colleagues on the use of the body plethysmograph. Together, these two papers hold the record as the fourth most-cited articles (3,109 times as of this writing) in the entire archi...
Airway resistance is measured in a somewhat similar way. The patient is asked to make rapid shallow breaths and, during inspiration, as the alveolar gas slightly expands, the box pressure rises slightly. This allows alveolar pressure to be calculated. The difference between alveolar and mouth pressure divided by flow rate is equal to airway resistance. A diagram of the apparatus is shown in Figure 4 (2).

The publication reported that the mean airway resistance of 21 normal subjects was 1.5 cm H₂O per liter per second at a flow rate of 1 liter per second panting, the standard deviation being ± 0.49. Measurements made on the same subjects on different days showed good reproducibility. Marked increases in airway resistance were seen in patients with airway obstruction in, for example, some cases of asthma, emphysema, and pneumocystosis. One patient aged 51 with silicosis had an airway resistance of 10.8 cm H₂O per liter per second for a flow rate of 0.5 liters per second.

As with so many advances, there had been attempts to use body plethysmography before these classic studies. In fact, the eminent German physiologist Eduard Pflüger (1829–1910) described a “pneumonometer” as far back as 1882 (3). But there were many technical difficulties to be overcome. Jere Mead, in a historical account of pulmonary mechanics, pointed out that when a subject breathes inside a closed chamber, the pressure of the chamber is altered by three factors: the increase in temperature as a result of body heat, the change in the number of gas molecules as oxygen is taken up and carbon dioxide is eliminated, and any change in volume of some part of the gas (4). It is only the last effect that is of interest; the rest is noise. DuBois’s contribution was to show that the signal-to-noise ratio could be vastly improved by the simple expedient of having the subject breathe shallowly and rapidly. That was the crucial step. DuBois’s mentor, Comroe, was aware of the potential of body plethysmography for measuring airway resistance and lung gas volume and had the expensive equipment on hand when DuBois arrived (Figures 1 and 2). According to DuBois, when he moved in and quickly showed the way, “Julius was pleased it worked, but irritated that it only took a week.”

For readers who would like to know more about the genesis of these two papers, we are fortunate to have a first-hand account by DuBois in the series “How it really happened,” published in the American Journal of Respiratory and Critical Care Medicine (5). There he describes how the body box sat in a corner gathering dust because various investigators had not been able to overcome the technical problems but how in December 1953 the box was moved into a room and DuBois with it, in case he wanted to try his hand. Fortunately, he had the necessary background in fluid dynamics and mathematics together with the clinical skills needed to deal with patients with airway disease, and he describes the enormous “eureka” moment when he eventually got the pesky machine to work.

From a historical viewpoint, these articles are remarkable for several reasons. First, the methods described for measuring lung volume and airway resistance are still employed on an everyday basis in dozens of clinical pulmonary function laboratories throughout the world. How often can that be said of a methods paper published nearly 50 years ago?

A second interesting point is that it is very unlikely that the JCI would publish such articles today. For one thing, it is probable that not many present-day readers of the JCI would be interested in these papers or even be able to understand them. Such has been the burgeoning of molecular medicine over the last twenty years that areas such as physiology have
been largely displaced. As an example, we have a strong Ph.D. program in biomedical sciences at UCSD which covers immunology, molecular biology, pharmacology, and physiology, but you would probably be hard put to find a graduate student who knew the meaning of adiabatic expansion of a gas, or the counterintuitive fact that the viscosity of a gas is independent of its pressure. A related trend is that our medical students taking their first-year physiology course are sadly ignorant of elementary concepts in physics such as pressure, flow, resistance, inertia, and compliance. As in many other medical schools, our dean rules over an empire where the concrete never sets as more buildings devoted to molecular biology rise up like mushrooms. If you wanted to find students interested in the concepts described in these two classical papers, you would have to walk to the other side of the campus to the School of Engineering where the Department of Bioengineering is very active but far removed from the Medical School.

Finally, it is remarkable that these articles were submitted to the JCI and accepted so quickly (the first article took only 28 days from submission to acceptance). The primary journals at the time for articles on lung mechanics were those of the American Physiological Society, notably the Journal of Applied Physiology, and most of the classic papers in that area can be found there. The field was dominated by people such as Fenn, Rahn, and Otis at the University of Rochester and Mead and Whittenberger at the Harvard School of Public Health. However, Comroe had a strong interest in what is currently called translational physiology, although that now-fashionable term would have been laughed at in the 1950s. Essentially every research project we embarked on then had its origins in some clinical or at least human problem. Comroe always had a great interest in the clinical potential of research and the first edition of his book The Lung (6) had an enormous impact and, incidentally, persuaded me to choose pulmonary medicine/physiology as a career.

In conclusion, it was a happy thought to include these two classical papers in the 80th birthday celebrations of the Journal. Those of us interested in respiratory physiology will get much pleasure from revisiting these classic studies that have influenced clinical pulmonary function testing to such an extent, and those readers with other interests will be reminded that biomedical research has many important areas beyond the molecular.

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