ONE OF THE FEW GOOD THINGS to come out of World War II was a dramatic increase in our understanding of respiratory physiology and, in particular, pulmonary gas exchange. In some instances the circumstances were peculiar. As has been pointed out elsewhere (2), one of the major centers for this work at the University of Rochester, New York, had inauspicious beginnings. Wallace Fenn was working on muscle contraction and potassium movement across cell membranes, Hermann Rahn (Fig. 1) was developing a bioassay method in frogs for pituitary hormones, and Arthur Otis was studying the activation of the enzyme tyrosinase in grasshopper eggs. Yet because of the exigencies of war these three were asked by the U.S. Air Force (USAF) to study the “physiological effects of pressure breathing” in the hope of improving the performance of pilots at high altitude. Although none of the protagonists had apparently had any previous training in human physiology and, it is said, were vague about the subdivisions of lung volume, this group laid the foundations of the modern understanding of pulmonary gas exchange and mechanics.

The other thread in the story came from an equally unlikely source. Joseph Lilienthal at the U.S. Naval School of Aviation Medicine in Pensacola, Florida, was asked to investigate carbon monoxide levels in the blood of pilots because this was thought to be a possible contributor to the large number of fatal crashes during training. He was using the microsyringe analyzer recently developed by Scholander and Roughton (10), and Richard Riley (Fig. 2), whose office was across the hall, had the idea that it might be possible to measure the Po2 and Pco2 of arterial blood by equilibrating a small bubble of gas.
with blood and analyzing this in the syringe (9). This sparked Riley’s interest in the mechanisms of hypoxemia in lung disease and led to a study of the role of ventilation-perfusion inequality. A related anecdote is that Riley developed pulmonary tuberculosis in 1948 and, while resting at home, reflected on the mysteries of ventilation-perfusion inequality, corresponded with the Rochester group, and developed his influential four-quadrant diagram. As he said, “Never was enforced confinement given more profitable psychotherapy” (6).

As a result of the discoveries of these two groups of investigators, the American Journal of Physiology and the Journal of Applied Physiology have the distinction of publishing the seminal papers on ventilation-perfusion relationships (1, 4, 7, 8). Unhappily, V\(\dot{A}\)/Q inequality (to use the argot of the initiated) is not fashionable at the present time, but to me it is one of the most elegant and satisfying areas in the whole of pulmonary gas exchange. I fell in love with the topic, as did many others, and my car license plate still says VAQ.

As implied above, the two groups and their disciples, Fenn, Otis, and Rahn in Rochester and then Buffalo on the one hand, and Riley and his colleagues in Pensacola and subsequently at Johns Hopkins on the other, came at the problem from different directions. The Rochester group under contract with the USAF started with attempts to better understand pulmonary gas exchange at high altitude, and indeed their emphasis continued to be on the gas side of the pulmonary blood-gas barrier and in particular the development of the enormously powerful oxygen-carbon dioxide diagram (5). By contrast, Riley and his colleagues began with the factors determining the arterial PO\(_2\), and the four-quadrant diagram, for example, emphasized the roles of the oxygen and carbon dioxide dissociation curves. They went on to develop a three-compartment model of pulmonary gas exchange where one compartment was “ideal” in the sense that gas exchange was optimal, another compartment had unperfused alveoli, and a third had unventilated alveoli. This model was the gold standard for assessing ventilation-perfusion inequality in patients with lung disease until the 1950s. In the sense that gas exchange was optimal, another compartment was largely independent and followed different courses, although apparently the two groups kept in touch. A feature of some of the early papers from both groups is that they are now difficult to read because of the awkward nomenclature. It was a major advance in 1950 when a committee chaired by John Pappenheimer agreed on the symbols that we still use today (3).

These papers show that the key to understanding pulmonary gas exchange in individual lung units is that the composition of the alveolar gas (and therefore the effluent blood) depends on only four primary factors: ventilation, blood flow, composition of inspired gas, and composition of mixed venous blood. Indeed the basic ventilation-perfusion ratio equation is deceptively simple:

\[
\frac{V_A}{Q} = \frac{8.63 \times R \times (C_{aO_2} - C_{VO_2})}{P_{ACO_2}}
\]

where \(V_A\) is alveolar ventilation, \(Q\) is blood flow (both in l/min), \(R\) is respiratory exchange ratio, \(C_{aO_2}\) and \(C_{VO_2}\) are the oxygen concentrations in effluent and mixed-venous blood (in ml/dl), and \(P_{ACO_2}\) is the alveolar Po\(_2\) (Torr).

The problem comes in implementing this equation because the solution depends on the oxygen and carbon dioxide dissociation curves, which are not only nonlinear but interdependent. This is the reason why the study of ventilation-perfusion relationships relied heavily on graphical analysis (5) until numerical solutions became possible with the advent of the computer (12).

The four papers on which this short essay is based will remain classics because an understanding of ventilation-perfusion relationships will always be important in analyzing pulmonary gas exchange in normal lungs under unusual conditions, such as at high altitude, and is the cornerstone for dealing with abnormal gas exchange in patients with lung disease. The American Physiological Society can rightly be proud of its role in developing this fundamental area of knowledge.

REFERENCES