The period from 1905 to 2004 was a particularly important era in the history of pulmonary gas exchange. The dramatic increase in knowledge from rudimentary ideas at the beginning of the 20th century to today’s sophisticated analyses might be compared with the progress from the Wright flyer at Kitty Hawk in December 1903 to modern supersonic aircraft. However, I cannot resist the temptation to peek back one page to the beginning of the 19th century because in some ways that sets the stage for 1905.

THE SETTING

Antoine Laurent Lavoisier (1743–1794) had the distinction of identifying the three respiratory gases in 1777: “Eminently respirable air [he later called it oxygene] that enters the lung, leaves it in the form of chalky aeriform acids [CO₂] . . . in almost equal volume. . . . Respiration acts only on the portion of pure air that is eminently respirable . . . the excess, that is the mephitic portion [nitrogen], is a purely passive medium. . . . The respirable portion of air has the property to combine with blood and its combination results in its red color” (1). Subsequently, Lavoisier emphasized the similarity between respiration and combustion stating that “respiration is nothing but a slow combustion of carbon and hydrogen, similar in all respects to that of a lamp or a lighted candle, and from this point of view, animals which breathe are equally combustible substances burning and consuming themselves.” Incidentally, the English novelist Charles Dickens was arguably influenced by this when he had one of his characters in Bleak House die by spontaneous combustion (2).

However, Lavoisier with his colleague Laplace made one major error when they stated that the combustion (oxidation) took place in the lung itself. In fact, it is remarkable that the identification of where the actual energy metabolism occurred proved to be extremely elusive, being a central problem in physiology for much of the 19th century. It was only in the 1870s that Eduard Pflüger (1829–1910) and his coworkers showed conclusively that metabolism takes place in peripheral tissues and that the blood simply transports the respiratory gases. By 1905, the gas exchange function of the lung was firmly established, and the carriage of oxygen and carbon dioxide by the blood had been largely worked out, although for example, the effects of pH and temperature on the oxygen dissociation curve were not elucidated until the 2nd decade (3, 4), and it was not until as late as 1967 that the role of 2–3 diphosphoglycerate on the oxygen affinity of hemoglobin was appreciated (5, 6).

OXYGEN SECRETION

One of the most colorful controversies in the first decade of the 20th century concerned how oxygen moved across the pulmonary capillary wall into the blood. Was this by passive diffusion or active secretion? Christian Bohr (1855–1911) (Figure 1) was a major proponent of the secretion ability of the lung, and in 1909, he referred to this as the lung’s “specific function” (7), although oddly enough in the same article he developed the mathematical basis for diffusion of oxygen across the pulmonary capillary, now known as the “Bohr integration.” Incidentally, Bohr has the unusual distinction of having his name attached to three different areas of pulmonary gas exchange: the Bohr integration, the Bohr dead space, and the Bohr effect (reduction of the oxygen affinity of hemoglobin caused by an increase in P{CO₂}). J.S. Haldane (1860–1936) visited Bohr’s laboratory and became one of the champions of oxygen secretion stating for example, “In the animals investigated the normal oxygen tension in the arterial blood is always higher than the alveolar air, and in some animals higher than the inspired air. The absorption of oxygen by the lungs thus cannot be explained by diffusion alone” (8).

Haldane subsequently led the influential Anglo-American Expedition to Pikes Peak, Colorado, in 1911 and believed that he obtained further evidence for oxygen secretion (9). Even today it is not clear precisely where the measurements were erroneous. In fact, Haldane continued to believe in oxygen secretion until his death in 1936 in spite of mounting evidence against the theory, and in the second edition of his book Respiration, he devoted an entire chapter to the subject (10). Haldane pointed out that secretion of several substances against concentration gradients (i.e., by active transport) occurs in many glands and that in the swim bladder of fishes the P{O₂} is often much higher than in the surrounding water. Because the swim bladder, similar to the lung, is an outgrowth of the gut, he reasoned that oxygen secretion could be expected.

August Krogh (1874–1949) (Figure 2) was one of the most articulate opponents of the secretion theory, and there is a memorable passage at the beginning of one of his articles that was published a year before Bohr died (11). Krogh developed an accurate tonometer in which a small air bubble was equilibrated with flowing blood and showed that the arterial P{O₂} was always lower than the alveolar value in a variety of animal experiments. Because Bohr had been one of the most ardent supporters of the secretion theory and Krogh was his student, Krogh’s introduction required all of the tact that he could muster: “I shall be obliged in the following pages to combat the views of my teacher Prof. Bohr on certain essential points and also to criticize a few of his experimental results. I wish here not only to acknowledge the debt of gratitude which I, personally, owe to him, but also to emphasize the fact . . . that the real progress, made during the last twenty years in the knowledge of the processes in the
Figure 1. Christian Harald Lauritz Peter Emil Bohr (1855–1911). This eminent Danish physiologist is remembered in the Bohr dead space, Bohr effect, and Bohr integration. He strongly believed in oxygen secretion by the lung. Courtesy of the Medical History Museum, University of Copenhagen, Denmark.

lungs, is mainly due to his labours” (11). Subsequently, Joseph Barcroft (1872–1947) led an expedition to Cerro de Pasco, Peru in 1921–1922 and showed that the arterial $P_{O_2}$ was always less than the alveolar value in humans (12). He also made the important observation that the arterial oxygen saturation fell during exercise at high altitude and argued that this could be explained by the failure of equilibration of $P_{O_2}$ between alveolar gas and pulmonary capillary blood. This was one of the first direct demonstrations of diffusion limitation in normal lungs at high altitude, a finding that has been confirmed many times since.

### DIFFUSING CAPACITY OF THE LUNG

One of the reasons for the theory of oxygen secretion was that it seemed impossible to explain oxygen transfer by the lung at high altitude. For example, in 1909, which was the same year when Bohr’s classic article, cited previously here, appeared, the Duke of the Abruzzi reached the extraordinary altitude of 7,500 m in the Karakorum mountains without supplementary oxygen. This astonished alpinists and physiologists alike. Only a few years before, an experienced mountaineer had reported that 21,500 ft (6,500 m) was “near the limit at which man ceases to be capable of the slightest further exertion” (13). Haldane and his colleagues calculated the alveolar $P_{O_2}$ of the Duke to be only 30 mm Hg, and they concluded that adequate oxygenation of the blood would be impossible based on passive diffusion, and therefore, oxygen secretion must have occurred (9).

However, August Krogh’s wife, Marie (Figure 2), developed a method for measuring the diffusing capacity of the lung using inhaled carbon monoxide. Her technique was essentially the same as the single-breath method employed in pulmonary function laboratories today. Her measurements showed that Haldane and his colleagues had markedly underestimated the diffusing capacity of the lung, and therefore, it was not necessary to resort to the oxygen diffusion hypothesis. Marie Krogh’s method of measuring the diffusing capacity did not become practicable for clinical work because of the difficulty of measuring the carbon monoxide concentration. However, with the introduction of the infrared CO meter, which was developed during World War II, there was renewed interest in the diffusing capacity, and Bates developed a steady-state technique (14), while the original Krogh single-breath method was slightly modified and popularized (15). Subsequently, Roughton and Forster (16) showed that it was possible to separate the two components determining uptake of oxygen across the blood–gas barrier; that caused by the diffusive properties of the alveolar membrane on the one hand and that due to the finite rate of uptake of oxygen by the hemoglobin in the red blood cell. The measurement of the diffusing capacity of the lung using carbon monoxide became an important test in the pulmonary function laboratory and is still extensively used today. A colorful application was the demonstration of an increased diffusing capacity in orbiting astronauts resulting from the movement of blood from dependent regions of the body into the lung as a result of the weightlessness (17).

### VENTILATION/PERFUSION INEQUALITY

We can now turn from oxygen secretion and diffusion to another mechanism that is fundamental to understanding pulmonary gas exchange, that is, ventilation–perfusion inequality. One of the first realizations that the gas exchange that takes place in any lung unit is determined by the ratio of ventilation to blood flow was that by Krogh and Lindhard (18) when they wrote this: “If the different lobes of the lungs are not equally dilated during inspiration the air in them must obtain a different composition and this must be true both with regard to $O_2$ and $CO_2$ during
normal breathing and with regard to other gases during special mixing respirations.” They then added in a prescient footnote this: “Unless, indeed, the circulation through each lobe should be in proportional to its ventilation.” A little later Haldane (19) stated that mismatching of ventilation and blood flow was a potential cause of hypoxemia, but unfortunately, he concluded that it would not cause carbon dioxide retention, a serious misconception that still surfaces from time to time.

However, the key advances in understanding ventilation–perfusion inequality came out of World War II, and the circumstances are fascinating. One principal group led by Wallace Fenn (1893–1971) was in the Department of Physiology at the University of Rochester, New York. They included Fenn himself who was working on muscle contraction and potassium movement across cell membranes, Hermann Rahn who was developing a bioassay method in frogs for pituitary hormones, and Arthur Otis who was studying the activation of the enzyme tyrosinase in grasshopper eggs (Figure 3). This seems like an unlikely group to revolutionize pulmonary gas exchange. Because of the demands of war, however, Fenn was asked by the U.S. Air Force to investigate the physiologic effects of pressure breathing at high altitude in the hope of improving the performance of airmen. The result was that although none of the three physiologists were trained in human physiology and, it is alleged, were vague about the definition of residual volume, in a few years, they had made fundamental discoveries in both pulmonary gas exchange and mechanics.

The other source was perhaps equally surprising. At the U.S. Naval School of Aviation Medicine in Pensacola, Joseph Lilienthal was investigating possible carbon monoxide poisoning in pilots as an explanation for the high frequency of fatal accidents during training. To measure CO levels in blood, he was using the microsyringe analyzer developed by Scholander and Roughton (20) whereupon Richard Riley (1911–2001) (Figure 4), who was working across the hall, saw the syringes and wondered whether it might be possible to determine the $P_{O_2}$ and $P_{CO_2}$ of arterial blood by equilibrating a small bubble of gas with the blood. He was successful in this (21) and thus developed his interest in the mechanisms of hypoxemia in lung disease and the role of ventilation–perfusion inequality. There is a nice anecdote here that resulted from Riley developing pulmonary tuberculosis in 1948. Fortunately, he was allowed to rest at home but of course had a good deal of time on his hands. His story is that he spent much of his time exploring the intricacies of ventilation–perfusion relationships, manipulating his four-quadrant diagram and occasionally contacting Rahn by mail. Riley remarked that “never was forced confinement given more profitable psychotherapy” (22). An interesting aside is that although many of us always regard Riley as a giant in the area of pulmonary gas exchange, he always claimed that his major research contribution was on the airborne transmission of pulmonary tuberculosis (23).

It is remarkable that the two groups worked essentially independently, although they communicated from time to time. Because the Rochester group (who later continued the work in Buffalo) started with the problem of pressure breathing, they tended to emphasize the gas side of the blood–gas barrier and, for example, developed the enormously powerful oxygen–carbon dioxide diagram (24). This was initially used to analyze the effects of high altitude, hyperventilation, and oxygen breathing on alveolar

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**Figure 4.** Richard Riley (1911–2001). His contributions to pulmonary gas exchange included the bubble technique for measuring arterial $P_{O_2}$ and $P_{CO_2}$, the concept of ideal alveolar $P_{O_2}$, and the three-compartment model. He also did important work on the airborne transmission of pulmonary tuberculosis.
gas composition, although the group certainly recognized that it could also be used to predict changes in the arterial blood gases. In contrast, Riley who came from a clinical training in Andre Cournand’s laboratory at Bellevue Hospital in New York City was particularly interested in the causes of hypoxemia in lung disease, and he and his colleagues tended to concentrate on the blood side of the barrier. They developed the elegant four-quadrant diagram based on the oxygen and carbon dioxide dissociation curves and went on to derive the three-compartment model of pulmonary gas exchange where one compartment is “ideal” in the sense that gas exchange is optimal, a second compartment has unperfused alveoli, and the third has unventilated alveoli. This model was the gold standard for assessing ventilation–perfusion inequality in patients with lung disease until the introduction of the multiple inert gas elimination technique, which allowed distributions of ventilation–perfusion ratios to be described (25).

One of the reasons that diagrams such as the O2–CO2 diagram of Rahn and Fenn (24) and the four-quadrant diagram of Riley and Cournand (26) were so valuable is that the oxygen and carbon dioxide dissociation curves are not only nonlinear but also interdependent. The result is that the equations relating PO2 and PCO2 to the ventilation–perfusion ratio cannot be solved algebraically, and therefore, graphical methods had to be employed. An important breakthrough occurred in the mid-1960s when first Kelman (27) and then Olszowka and Farhi (28) introduced digital computer procedures for describing the oxygen and carbon dioxide dissociation curves. Perhaps I can be allowed a little personal recollection here. When I first saw Kelman’s subroutines demonstrated at a meeting of the Physiological Society in the United Kingdom in the early 1960s, I realized that this meant that the tedious graphic methods of analyzing ventilation–perfusion relationships would soon be supplanted by computer analyses. However, when I subsequently developed a computer model of the lung containing ventilation–perfusion inequality during a sabbatical year at the NASA Ames Research Center (29), we had a visit from a Presidential Science Advisory Committee, including Wallace Fenn himself, and I proudly showed him a computer solution for a ventilation–perfusion ratio equation. Much to my chagrin, he seemed to be completely unimpressed, but these computer techniques eventually led to the development of the multiple inert gas elimination technique (25). Here, a major advance was the realization that the normal respiratory gases, oxygen and carbon dioxide, have a very limited ability to give information about patterns of ventilation–perfusion inequality, and much more information became available when the gas exchange of a series of inert gases having a range of solubilities was exploited. However, the multiple inert gas-elimination technique only became feasible because of the mathematical expertise of Peter Wagner and his colleague John Evans (30) but has now become the gold standard for assessing ventilation–perfusion inequality.

**ARTERIAL BLOOD GASES**

The multiple inert gas elimination technique for determining distributions of ventilation–perfusion ratios primarily remains a research tool because of its complexity. The main armament in the trenches for assessing abnormal pulmonary gas exchange remains the measurement of the arterial blood gases with blood-gas electrodes, and their development constitutes one of the most important advances of the last 100 years. In fact, when I tell medical students that when I was a young resident we could not measure arterial PO2, PCO2, or pH, they stare at me in disbelief. Those were the days when considerable importance was given to the detection of cyanosis as an index of impaired gas exchange. Who knows how many patients with chronic obstructive pulmonary disease died when they were given oxygen to relieve their cyanosis and they developed lethal carbon dioxide retention.

One of the first measurements of the amounts of oxygen and carbon dioxide in blood was by Gustav Magnus (1802–1870), who used his new mercury pump to expose the blood to a partial vacuum (31). His demonstration that arterial blood had more oxygen and less carbon dioxide than venous blood helped to dispel the erroneous notion that the metabolic combustion (oxidation) took place in the lungs. Improvements in gasometric analysis of blood were made by Carl Ludwig and Eduard Pflüger, but the methods were not used in clinical medicine. A major advance was the development of arterial puncture because before this it was not practicable to obtain arterial blood. The first arterial punctures in humans were made by Hürter (32), and he was able to show that the arterial oxygen saturation in four normal subjects was between 93% and 100%. However, the significance of his work was overlooked until Stadie introduced the technique at the Rockefeller Institute where he investigated the relationship between arterial oxygen saturation and cyanosis in patients with pneumonia (33). These early measurements of arterial oxygen saturation were made by vacuum extraction of the blood gases and their subsequent manometric or volumetric analysis, as described by Van Slyke and O’Neill (34). Reference has already been made to the Riley bubble technique for measuring both arterial PO2 and PCO2, and this gave a great stimulus to the understanding of pulmonary gas exchange. However, the technique was technically demanding, and many potential “bubblers” were forced to make the pilgrimage to Johns Hopkins to learn the intricacies at firsthand.

The measurement of arterial PO2 was revolutionized by the introduction of the polarographic oxygen electrode. The first of these was the “dropping mercury cathode,” which worked because the continuously renewed surface of the drops avoided inactivation of the electrode by proteins in the blood. A dropping mercury electrode was successfully used by Berggren (35) to measure alveolar–arterial PO2 differences in a series of normal subjects. However, the device was difficult to use and never became a clinical instrument. The breakthrough was the introduction of the platinum electrode by Leland Clark and colleagues (36). In the original version, a small platinum electrode was covered with cellophane and immersed in a sample of blood. However, these early devices suffered from errors caused by oxygen depletion near the electrode unless the blood was rapidly stirred. This problem was later avoided by using a very small electrode tip.

Shortly after the development of a clinically useful oxygen electrode, Severinghaus and Bradley (37) described an electrode for measuring PCO2 in blood. The principle was that carbon dioxide diffused from the blood through a Teflon membrane into a small volume of electrolyte solution in which the pH was measured with a glass electrode. Both the PO2 and PCO2 electrodes were incorporated into a common thermostat. In fact, Stow and coworkers (38) had previously demonstrated the possibility of measuring the PCO2 of blood by wrapping a thin rubber membrane over a film of distilled water around a glass pH electrode, but this suffered from severe instability. This problem was overcome by Severinghaus and Bradley when they added bicarbonate to the electrolyte.

The clinical measurement of blood pH predated both the oxygen and carbon dioxide electrodes. An important stimulus here was the polio epidemics of 1950–1953, which resulted in patients with bulbar polio being treated by mechanical ventilation...
in “respirators,” as they were then known. These were heroic days before sufficient ventilators were available, and teams of medical students and others were employed to compress rubber bags manually during successive shifts over the 24 hours. It was anyone’s guess what the arterial Po2 was under these conditions.

Poul Astrup in Copenhagen first computed the Po2 from the Henderson–Hasselbalch equation by combining the plasma pH and CO2 concentration, the latter being determined in a Van Slyke apparatus. Actually, the first blood pH electrode went back to the 1920s and 30s, but it was too awkward to be used clinically. Astrup subsequently developed a simpler method for measuring Po2 by using the linear relationship between blood pH and log Po2, this being generated by equilibrating a plasma sample with gases of differing CO2 concentrations. As a result, the Po2 could be read from the measured pH. This work led to the introduction of the so-called standard bicarbonate, that is, the bicarbonate concentration at a normal Po2 (originally obtained by having the technician exhale over the sample!) and later the base excess.

**OXIMETRY**

Modern blood–gas electrodes play a critical role in a modern clinical respiratory laboratory, particularly in the intensive care unit. However, the relatively invasive arterial puncture is now supplemented by measurements of arterial oxygen saturation by oximetry. The principle of this goes back to Hoppe-Seyler, who crystallized and named hemoglobin and showed that oxygen changed its color. Various devices to measure the color of the blood were developed over the years, particularly by Millikan in the United States and Kramer in Germany during World War II. Millikan described an ear oximeter apparently largely based on German research, and this was subsequently improved by Earl Wood who added a pressure device to squeeze blood out of the ear and thus obtain a zero setting. The arterial oxygen saturation was measured using a string galvanometer, and on a personal note, I made a large series of measurements with this very fragile device in the Silver Hut expedition in the Himalayas at an altitude of 5,800 m in 1960–1961.

The ear oximeter was cumbersome, and a big advance was made by Takuo Aoyagi in 1972 when he developed the pulse oximeter, which could be used on the finger. This device is now used very extensively in the clinical environment with enormous value.

**CONCLUSIONS**

Gas exchange is the primary function of the lung, and many patients with pulmonary disease have impaired gas exchange that can progress to respiratory failure and death. It is therefore very satisfying to be able to review the enormous advances that have taken place in the last 100 years. Nevertheless, it is worth pointing out that important areas of ignorance remain. For example, a critically ill patient in the intensive care setting often has grossly disturbed pulmonary gas exchange, but many aspects of their care are poorly understood. Just to take one example, altering the levels of positive end-expiratory pressure and/or the inspired oxygen concentration will often improve the arterial Po2, but many of the changes within the lung after these interventions are obscure. Furthermore, with the modern emphasis on molecular biology, much of the attention that was devoted to pulmonary gas exchange has moved away, and an entire generation of young pulmonary physicians are sadly ignorant of this area. Presumably, the pendulum will swing back in due course, and more interest will be directed at this critically important and fascinating area of pulmonary medicine.

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