Centennial Review

Pulmonary Hypertension

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The modern era in cardiopulmonary medicine began in the 1940s, when Cournand and Richards pioneered right-heart catheterization. Until that time, no direct measurement of central vascular pressure had been performed in humans. Right-heart catheterization ignited an explosion of insights into function and dysfunction of the pulmonary circulation, cardiac performance, ventilation–perfusion relationships, lung–heart interactions, valvular function, and congenital heart disease. It marked the beginnings of angiocardiography with its diagnostic implications for diseases of the left heart and peripheral circulation. Pulmonary hypertension was discovered to be the consequence of a large variety of diseases that either raised pressure downstream of the pulmonary capillaries, induced vasoconstriction, increased blood flow to the lung, or obstructed the pulmonary vessels, either by embolism or *in situ* fibrosis. Hypoxic vasoconstriction was found to be a major cause of acute and chronic pulmonary hypertension, and surprising vasoreactivity of the pulmonary vascular bed was discovered to be present in many cases of severe pulmonary hypertension, initially in mitral stenosis. Diseases as disparate as scleroderma, cystic fibrosis, kyphoscoliosis, sleep apnea, and sickle cell disease were found to have shared consequences in the pulmonary circulation. Some of the achievements of Cournand and Richards and their scientific descendents are discussed in this article, including success in the diagnosis and treatment of idiopathic pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, and management of hypoxic pulmonary hypertension.

Keywords: high altitude; hypoxic vasoconstriction; primary pulmonary hypertension; pulmonary arterial hypertension; thromboembolism

THE BIRTH OF MODERN CARDIOPULMONARY MEDICINE: COURNAND AND RICHARDS

The inaccessibility of the pulmonary circulation to direct study was the major impediment to progress in cardiopulmonary research to the midpoint of the 20th century. The field of cardiology was largely limited to the stethoscope, the electrocardiogram, and the autopsy suite. An understanding of pulmonary physiology had advanced through the efforts of multiple investigators, including Christian Bohr, the Kroghs, J. S. Haldane, and L. J. Henderson (1). Henderson summarized the state of knowledge in his treatise *Blood: A Study in General Physiology* (2), and he proposed the simple but essential concept that "the lungs, heart and circulation should be thought of as a single apparatus for the transfer of oxygen and carbon dioxide between the atmosphere and the working tissues."

But, to accurately measure gas exchange and the matching of perfusion and ventilation in the lung, the return of blood to and delivery from the chest, crucial information was missing. Measures of mixed venous gas tensions of oxygen and carbon dioxide from the right atrium were necessary but unavailable, and cardiac output could only be estimated. The Fick method of calculating cardiac output was highly inaccurate without venous sampling, and the CO_2 rebreathing method required cumbersome measurements that failed in patients with uneven distribution of ventilation and perfusion. Pulmonary vascular pressures in humans were simply a mystery.

In the 1930s, Dickinson W. Richards and Andre F. Cournand, of the Bellevue Service of Columbia University College of Physicians and Surgeons, attacked the mysteries of lung function and gas exchange, and developed techniques, such as nitrogen washout, and the estimates of residual volume and total lung capacity (3, 4). These investigators began as pulmonary physiologists, but it became evident that direct cardiac measurements would be essential for further progress. They were aware of the report of Werner Forssman, a German physician who had catheterized himself in 1929 via the antecubital vein and published a picture of the catheter in his heart (5). It is difficult to imagine now how the entire medical establishment of that era so strongly believed that placement of a cardiac catheter was likely to result in morbid or fatal complications. Forssman's experiment flew in the face of the best clinical judgment of the era, and it damaged his career (6). Cournand and Richards saw the enormous potential of this technique, and began experiments placing catheters in the right atrium of dogs, chimpanzees, and finally humans, in 1940, to measure blood gas content (7). The experiments succeeded and the catheters were found to be safe. Not infrequently, a catheter would advance to the right ventricle and pulmonary artery, where pressures were measured. The surprising discovery of highly variant pressures and flow in health and disease, the capacity to dissect ventilation–perfusion relationships, the descriptions of the pathophysiology of valvular abnormalities and congenital heart defects, and the advent of angiography all emerged in an explosion of new information in the 1940s and 1950s after the publication of this work (1, 3, 4, 6). Much of the new information about pulmonary circulation and the heart was discovered in the Bellevue laboratories and by men and women who had studied with Cournand and Richards and were their scientific descendents. Subsequent trainees of their own fellows populate university programs throughout the world.

Forssman, Cournand, and Richards won the Nobel Prize in 1956 in physiology and/or medicine for their contributions to the understanding of the circulation. It is frequently stated that they won the Nobel Prize for being the first to perform right-heart catheterization in humans. That is only partly true. They won because they led a revolution in cardiopulmonary medicine that continues to this day.

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BRIEF HISTORY OF THE PULMONARY CIRCULATION BEFORE COURNAND AND RICHARDS

The origin of modern Western cardiology dates to the publication of William Harvey's *Exercitatio Anatomica de Motu Cordis et sanguinis in Animabilus* in 1628 (8). By careful observation of the flow of blood in vessels and by dissection, Harvey correctly established that the blood circulates from the heart to the tissues via the arteries and thence back to the heart via the veins and through the lungs. Microscopy was not yet powerful enough to show flow in tissues, but Harvey deduced that there were pores in the lung that allowed the blood to return to the heart. Harvey also had the following remarkable insight about the function and limitation of the right ventricle compared with the left:

> So it appears that whereas one ventricle, the left, suffices for distributing the blood to the body and drawing it from the vena cava, as is the case in all animals lacking lungs, nature was compelled when she wished to filter blood through the lungs to add the right ventricle. . . . Thus, the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them.

The pores that Harvey proposed were shown under the microscope to exist as vascular capillaries by Malpighi in 1661 (9). Extensive measurements of pressure and flow in the circulation were first reported in 1733 by Stephen Hales, a pastor in Scotland, who catheterized hundreds of animals of multiple species under a variety of normal and stressed conditions (10). By direct cannulation of vessels and chambers, he made the first accurate measurements of left ventricular output, stroke volume, systolic and diastolic pressures, blood velocity, and pressure drop down the branching circulation. This astonishing body of information was achieved using straight glass tube manometers that were either blood or water filled, requiring vertical lengths of up to 10 ft for measurements of pressure in the systemic circulation. He also demonstrated and recognized the difference in pressure between the pulmonary and systemic circulation and the effect of ventilation on pressure and pulse.

Over the next 150 years, occasional descriptions of right ventricular involvement in disease were made by Morgagni in 1762 (1) and by Laennec in 1826 (1), who clearly described right-ventricular hypertrophy in two cases of emphysema. Virchow described several instances of multiple pulmonary embolism with dilated right ventricles in his monograph, *Thrombosis and Embolism* in 1846 (1). Connheim observed, in 1880 (1), that the pulmonary circulation is favored by normal respiration, impaired by positive-pressure respiration, and that pulmonary artery pressure in animals does not significantly increase until almost three-quarters of the vascular bed have been occluded. He also noted right-ventricular hypertrophy at autopsy in cases of multiple pulmonary emboli, extensive chronic bronchitis, and even extreme obesity. Any who feel pride in their diagnostic acumen must look over their shoulder at Connheim with humility. The medical literature of the United States of the early 1900s was far less advanced than that of Europe. Osler mentions sclerosis of the pulmonary artery as a consequence of emphysema and cites Romberg's case, which may have been the first description of primary pulmonary hypertension (PPH) (11). Osler listed causes of right ventricular hypertrophy as a consequence of mitral valve disease, emphysema, and obliteration of pulmonary arteries, but there is little discussion (12). The term "cor pulmonale" came into use in the first 30 years of the 20th century. In the American literature, the first mention in print was White and McGinn's use of "acute cor pulmonale" in cases of decompensated pulmonary embolism (13).

Thus, by the time Forssman had the temerity to prove that right-heart catheterization was safe in humans, and Cournand and Richards were struggling to advance the field of cardiopulmonary physiology, much descriptive work had shown that measurement of pressure, flow, and gas content in the pulmonary circulation would be essential to understanding how multiple diseases lead to an increase in the "flesh" of the right heart.

PRIMARY PULMONARY HYPERTENSION: A MYSTERIOUS KILLER BEGINS TO YIELD

Romberg was the first to describe pulmonary arterial sclerosis in 1891, and the first systematic anatomic description was by Brenner in 1935 (14). In 1951, David Dresdale, a trainee of Cournand and Richards, first reported hemodynamic variables in cases of pulmonary hypertension without evident etiology, and coined the name "primary pulmonary hypertension" (15). This illness is now called idiopathic pulmonary arterial hypertension (PAH) (16). Because PPH did not have an accepted, unique name prior to Dresdale's publication, review of old charts and literature from before 1950 is unsatisfactory. In considering the reversibility of pulmonary hypertension in a variety of conditions, Paul Wood developed the concept of reactive pulmonary hypertension, especially in the context of responses to mitral stenosis, and hypothesized that there may be a vasoconstrictive factor in some cases of pulmonary hypertension (17). The spectrum of histopathologic changes in Eisenmenger's syndrome and in PPH was defined by Heath and Edwards in 1958 (18), focusing on the effects of overflow on the pulmonary circulation in congenital heart disease. The most complete description of PAH was made by Wagenvoort and Wagenvoort, in 1970, of 156 cases of pulmonary hypertension collected throughout Europe (19). Together, Heath, Edwards, and the Wagenvoorts developed a schema both of severity of arteriopathy by grades, and of the specific lesions, including concentric intimal fibrosis, medial hypertrophy, plexiform lesions, *in situ* thrombosis, and dilatation lesions. These anatomic descriptions continue to form the basis of studies of the pathogenesis of this disease. PPH was the topic of a World Health Organization meeting in Geneva in 1973, where clinical and pathologic understanding of the disease was first addressed by a consensus conference (20).

Idiopathic PAH is a rare disease, affecting approximately only one in one million persons in the population. But it is a cruel disease, frequently affecting otherwise normal young women with a median survival of 2.8 years when untreated (21). An epidemic of pulmonary hypertension occurred in Europe in the late 1960s related to the use of an appetite suppressant, aminorex, an episode that was echoed in the dexfenfluramine-phentermine experience in France and the United States in the 1990s (22). Many in the American Thoracic Society worked to prevent the use of these appetite suppressants and the morbid physical, social, and legal consequences that followed.

The accurate diagnosis and effective management of PPH is a medical triumph built by the collaborative effort of a number of clinical scientists over the last 20 years (23). From the first description by Dresdale until the late 1970's, there were numerous isolated reports of vasodilator efficacy in patients with PPH. The advent of effective calcium channel blockers, known to inhibit hypoxic vasoconstriction (24), and reports of efficacy of hydralazine fueled interest in aggressive management of this grim disease. A disciple of Cournand and Richards, Al Fishman, led the effort to establish a National Institutes of Health–funded registry, which defined the demographics, hemodynamics, survival, and management of PPH (21). Careful descriptions in the registry revealed the extent to which PAH is the consequence of multiple diseases, including immune vascular diseases, HIV infection, and portal hypertension. Even more importantly, it brought investigators together in collaboration, and the names

of many of the most important contributors to the management of this disease over the last two decades are among those who contributed to the project (21). By careful collaborative clinical trials, both functional status and survival were proven to be improved with the use of continuous infusion of intravenous epoprostenol, a synthetic salt of prostacyclin (25). This bold initiative was followed by the development of other formulations of prostacyclin and alternate delivery systems, including subcutaneous, aerosol, and oral, have shown promise in the treatment of idiopathic PAH (26, 27). The discovery of prostacyclin was cause for another Nobel Prize, to John Vane, and was propelled forward by the work of Moncada (28). Further progress has led to oral endothelin receptor antagonists and phosphodiesterase inhibitors that have proven efficacious in many patients and have reduced the need for the very expensive and complex intravenous epoprostenol (29, 30).

With more and more attention to the pathobiology of PPH, it seems likely that drugs will be developed over the next several years that will interdict signaling abnormalities that lead to the pulmonary vasculopathy. These areas of research are well described in reports of the World Health Organization's conference in Evian in 1998 and an international conference in Venice in 2003 dedicated to this disease (31). The patient- and family-based Pulmonary Hypertension Association is a robust, energetic entity that is highly supported by investigators in pulmonary hypertension. The Pulmonary Hypertension Association has recently entered into a research agreement with the American Thoracic Society to cofund investigations in pulmonary hypertension, a most auspicious development.

The genetic basis of PPH was recently discovered in studies from two laboratories (32, 33). In 1954, Dresdale reported two cases of PPH in a mother and son, and suggested that there might be a genetic basis. In 1984, detailed descriptions of all 14 reported families in the American literature showed that familial PPH had the same sex, age, and survival features as sporadic PPH (34). The discovery of the genetic basis of PPH required the confluence of two scientific processes: first, the development of family registries and the archiving of DNA; second, the revolution in molecular genetics and the completion of the human genome project. A member of the transforming growth factor-β family of receptors, bone morphogenetic protein receptor type 2 has been found to be mutated in approximately 75% of familial PAH, and in as many as 25% of cases of idiopathic PAH (35). In addition, mutations in ALK-1, another transforming growth factor-β receptor that causes hereditary hemorrhagic telangiectasia, have also been found to cause PAH (36).

These discoveries have propelled worldwide studies on the pathobiology of familial and idiopathic PAH, and are likely to yield clues to early diagnosis, treatment, and, ultimately, prevention of PAH. Thus, PAH has begun to yield to a growing group of clinical and basic scientists who have been fascinated by this enigmatic disease and appalled at its toll on otherwise healthy people.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION: TRIUMPH OF KEN MOSER'S TENACITY

Acute cor pulmonale is an unusual but potentially fatal complication of pulmonary thromboembolism. As a research fellow in the 1930s, John Gibbon witnessed the death of a young woman after an attempt at emergency surgical thrombectomy, and his development of the heart–lung bypass pump oxygenator was a response to that experience (37). Today, heart–lung bypass is the basis for life-saving treatment of a large variety of cardiopulmonary diseases, used on a scale almost unimaginable when Gibbon first conceived it. It is rarely used for acute thrombectomy, but is now part of life-saving treatment of a rare sequella of pulmonary embolism (Figure 1).

This rare complication of unresolved pulmonary embolism is chronic thromboembolic pulmonary hypertension (38). Chronic thrombotic pulmonary hypertension is a peculiar problem of unclear pathogenesis. To be afflicted with this condition, a person must first have one or more large pulmonary emboli, the emboli must not undergo full lysis over time, the emboli must fibrose to the intima in concentric lamina, and the degree of vascular obstruction must lead to sufficient pulmonary hypertension to

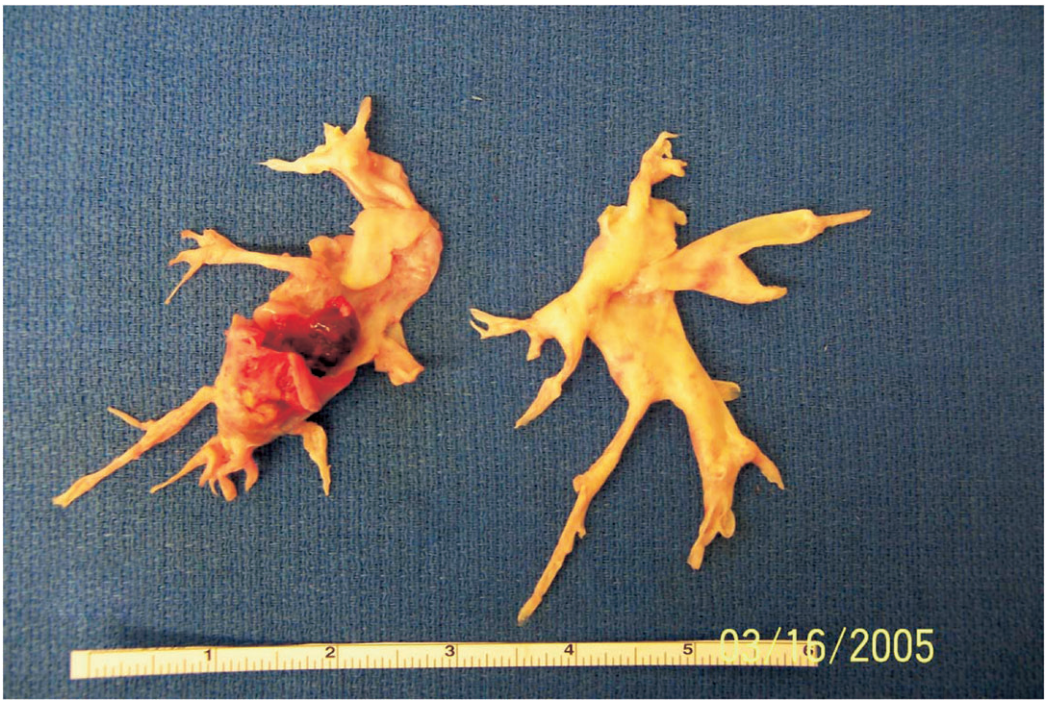

Figure 1. Fibrosed thrombus delivered from the pulmonary arteries by endarterectomy during cardiopulmonary bypass from a patient with chronic thromboembolic pulmonary hypertension. This life-saving procedure converts patient from New York Heart Association class IV to class II. Courtesy of William Auger, M.D.

cause right-heart failure. Thus, a number of potential abnormalities of thrombophilia, the lytic system, fibrogenesis, endothelial dysfunction, pulmonary vasoreactivity, and right-heart adaptability may contribute to pathogenesis. The pathogenesis of this condition is still enigmatic, with antiphospholipid syndrome being the only frequently diagnosed associated malady, in approximately 15% of cases (39). The interval between the initiating thromboembolic event and right-heart failure may be years to decades, making this condition a great mimic of other forms of pulmonary hypertension. This problem was identified in the 1950s and surgical management was attempted in the 1960s. The inexperience related to the small number of early cases led to a high failure rate, but Ken Moser, a young pulmonologist at Georgetown, believed in the procedure and pushed his surgical colleagues to explore and advance the medical and surgical management of this disease.

Ken Moser moved to the University of California at San Diego in 1969, and established a small program of surgical pulmonary thromboendarterectomy with a thoracic surgeon, Nina Braunwald. A look at his published reports attests to the success of the procedure and growth of the program. In 1965, Moser reported a single successful thromboendarterectomy with 30-month follow-up, and a second report of a single success in 1973 (40, 41). By 1983, he was able to report survival of 13 of 15 operated cases with marked improvement in functional status (42). By 2003, the group at San Diego reported on the experience and lessons learned from 1,500 cases, with a mortality rate that was reduced from 17% in the period between 1970 and 1990 to 4.4% between 1998 and 2002 (43). The mean improvement in pulmonary vascular resistance is from 10–12 Wood units preoperatively to approximately 3–5 units after the procedure, with an average reduction in New York Heart Association class from III-IV to I-II. The overall worldwide experience is now over 2,000 cases as other centers learn and take on this procedure. In addition to this surgical experience, the thromboendarterectomy program has established new standards in quantitative, accurate diagnosis of pulmonary vascular obstruction and has advanced our understanding of the pathology of pulmonary microvascular disease, right-heart responses, and postoperative management of patients with right-heart failure and abnormal pulmonary perfusion (43–45).

It could be argued that Ken Moser pioneered the most successful curative procedure in pulmonary medicine, against long odds of success and against widespread pessimism of the medical and surgical community. This is one of the triumphs in pulmonary medicine of the last 100 years.

HYPOXIA AND PULMONARY HYPERTENSION

Imagine the wonder that Cournand and associates felt when they first discovered that pulmonary arterial pressures were as much as four- to fivefold those of normal in patients with a variety of heart and lung diseases. The early notion that the circulation might be anatomically fixed in disease was quickly dashed by the observation that successful medical treatment resulted in reduction in pressure toward normal. Thus, a vasoconstrictive factor was hypothesized. Just at that time, in 1946, Von Euler and Liljestrand had published the report of hypoxia-induced pulmonary vasoconstriction in the cat, and they also made the elegant and accurate teleologic prediction that hypoxic vasoconstriction served to preserve ventilation–perfusion matching in conditions where regional ventilation was impaired (46). As an aside, Von Euler won the Nobel Prize, but not for hypoxic vasoconstriction. He won for the elucidation of the role of endogenous catecholamines in the circulation. In addition to all this, he also discovered prostaglandins—not a bad scientific hat trick (47).

Shortly after the report of Von Euler's work in the cat, Cournand and associates demonstrated that hypoxia was an effective pulmonary vasoconstrictor in humans (48), and also showed that acetylcholine was an effective but transient vasodilator (Figure 2) (49). The conundrum that a muscarinic constrictor could cause vasodilation of the hypertensive pulmonary vascular bed was solved 30 years later by the efforts of another group of Nobel laureates, Furchgott, Ignarro, and Murad, for the discovery of nitric oxide (50). Acetylcholine stimulates the release of nitric oxide from the pulmonary endothelium. If the endothelium is denuded, acetylcholine is a vasoconstrictor; if intact, vasodilation ensues.

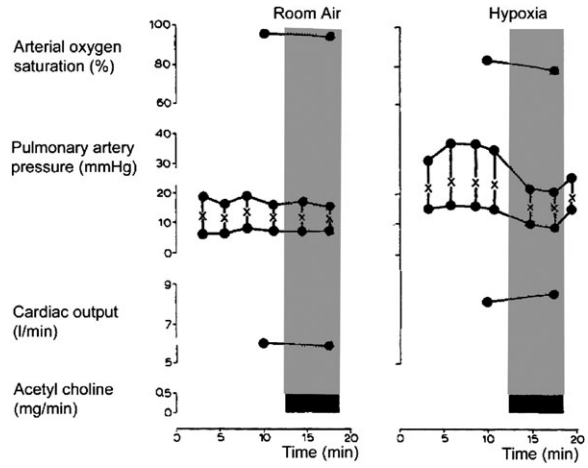

Figure 2. One of the first demonstrations of the effects of hypoxia on pulmonary arterial systolic and diastolic pressure and cardiac output in a human subject (49). Inhalation of a hypoxic gas mixture reduced oxygen saturation to approximately 80%, followed by hypoxic vasoconstriction and a mean pulmonary artery pressure rise of approximately 15 mm Hg. Acetylcholine had no effect on the unconstricted bed, but reduced pulmonary artery pressure toward normal during hypoxia. Thirty-five years later, the vasodilator effects of acetylcholine were found to be due to the release of endogenous nitric oxide.

The dawn of the age of hypoxic vasoconstriction in 1946 thus coincided with the ability to measure it in humans. The discovery of the wedge pressure by Dexter's lab, and the development of the balloon flotation pulmonary artery catheter by Swan and Ganz, made physiologic interpretation of pulmonary hemodynamics possible at the bedside (51, 52). Over the next two decades, it was rapidly determined that hypoxia was the primary cause of pulmonary hypertension in a wide spectrum of seemingly unrelated diseases, such as emphysema, kyphoscoliosis, sleep hypoventilation, cystic fibrosis, high-altitude pulmonary edema, and chronic mountain sickness (53, 54). The role of hypoxia in the fetal circulation and the transition to an oxygenated low-pressure system after birth was elucidated by Dawes and coworkers (53, 54). The additive role of acidosis in pulmonary vasoconstriction, usually related to CO_2 retention, the precapilliary (arteriolar) location, the interaction of the pulmonary circulation with downstream left-atrial and left-ventricular pressures, and the effects of pulmonary hypertension on the right ventricle were elucidated. It was clearly shown that the severity of pulmonary hypertension was directly related to the degree of hypoxia, in a curvilinear relationship that paralleled the oxyhemoglobin dissociation curve. There was a virtual geyser of new information about the role of hypoxia in pulmonary hypertension and cor pulmonale during the period of 1950–1970. Space does not permit discussion of the wonderful stories of high-altitude medicine (55), the scientific expeditions to Everest, the

Figure 3. Oxygen therapy in the 20th century was developed and used by Haldane. Barach used oxygen in patients with pneumonia in the 1920s, but routine use of oxygen therapy was not persuasive to the medical community until the late 1960s. Lest modern practitioners think that all effective therapies are modern, this drawing of the use of nasal prongs to deliver oxygen dates to 1907 (64).

understanding of sleep-disordered breathing, and achievements in managing pulmonary vascular disease of the newborn (56).

The mechanism of hypoxic vasoconstriction remains to this day unknown (56–58). Many potential explanations were quickly tested and discarded, and included sympathetic and parasympathetic nerves, catecholamines, serotonin, histamine, and—later—eicosanoids. Investigators over the last 15 years have focused more on cellular energetics, reactive oxygen species, oxygenases, and ion channels, but the fundamental mechanism of hypoxic vasoconstriction is still to be proven (57).

It is well established that oxygen is the most efficacious therapy for cor pulmonale related to alveolar hypoxia. The best proof came from two clinical studies, the Nocturnal Oxygen Trial and the European MRB trial (59, 60). Oxygen was found to improve both function and survival in chronic cor pulmonale in patients with chronic bronchitis and emphysema, and these studies form the basis of the current practice of continuous oxygen therapy. Experiments with therapeutic oxygen in the 20th century were started by J. S. Haldane and Alvin Barach (Figure 3) (61, 62). The modern use of oxygen in chronic lung disease was aggressively advanced by Petty (63). Because of the increased CO_2 retention that occurs in patients with severe lung disease given therapeutic oxygen, and because of occasional reports of accelerated respiratory failure in decompensated patients given oxygen, it was generally believed in the 1960s that oxygen therapy was dangerous and inappropriate. Today, oxygen therapy is the basis of improved functional capacity, quality of life, and survival in chronic lung failure, and is so commonly applied that it is difficult to remember the skepticism and reluctance of a prior age.

CONCLUSIONS

The function of the pulmonary circulation is central to many lung diseases as disparate as sickle cell anemia, sleep apnea, scleroderma, and postpolio syndromes. The common link is pulmonary hypertension, which results from vascular obstruction, overflow, back pressure, and vasoconstriction. The work of Cournand and Richards was the major milestone of the last 100 years in the pulmonary circulation, as it ushered in an explosion of understanding of gas exchange, congenital and valvular heart disease, chronic lung diseases, and the role of hypoxia. Many of the major advances in the pulmonary circulation were led by mavericks, such as Forssman, Moser, and Petty, who pursued their passion against prevailing opinion. It is hoped that the current century will see similar advances, with reversal and prevention of idiopathic PAH, and prevention of cor pulmonale in diseases such as sickle cell anemia, collagen vascular diseases, and other maladies that afflict humans.

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