Life at the Frontier

The Third Annual John W. Severinghaus Lecture on Translational Science

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Editor’s Note: In this article, the author, Warren M. Zapol, M.D., describes his life in translational medical research. His career has required building teams to improve therapy for respiratory failure, including the use of membrane oxygenators, developing inhaled nitric oxide, and studies of Weddell seals in Antarctica.

James C. Eisenach, M.D., Editor-in-Chief

For someone beginning a career in anesthesiology in 1970, there was no lack of problems to tackle. While the newly developed field of intensive care had proven capable of resolving simpler, easily reversed clinical conditions (e.g., temporary postoperative ventilatory insufficiency, atelectasis, transient coma), tougher problems—such as hypoxia in the newborn and adult due to acute respiratory distress syndrome, pneumonia, and sepsis—lay at the frontier of our specialty, posing significant challenges. Early on, I determined that, to make headway in these areas, it would be essential to build a multidisciplinary team that could explore the problem, develop and test solutions in the laboratory, and then, if warranted, at the bedside.

My introduction to research at the National Institutes of Health (NIH) in 1967 provided ample evidence to me that medical advances were being crafted by groups of scientists—often from widely separated fields, working in teams on tough problems. The days of the solo, Pasteur-like investigator, working in relative isolation to make major advances or shift paradigms, were over. I learned this key lesson from great mentors at their own scientific frontiers working in teams, and I applied it many times throughout my life.

NIH Pioneers

Team 1: Newborn Respiratory Support with an Artificial Lung

My surgical internship on the Harvard Surgical Service at Boston City Hospital, Massachusetts, in 1967 was interrupted by the Vietnam War. When I failed to get a deferment from the draft to complete my residency via the Berry Plan (a national physicians lottery), I interviewed for the Public Health Service.

Luckily, I was selected for a research slot in the Laboratory for Technical Development at the National Heart Institute (now the National Heart, Lung, and Blood Institute) in the NIH Clinical Center, Bethesda, Maryland. That fortuitous event gave me my first in-depth research experience in a large multidisciplinary group. The laboratory leader was Robert L. (“Bob”) Bowman, M.D. (1916–1995), a former student of the pioneering anesthesiologist Emery Rovenstine, M.D. (1895–1960). Bob invented a key instrument used in medical research in the 1970s, the Aminco-Bowman spectrophotofluorimeter (Aminco International, Inc., Lake Forest, CA). He had joined the National Heart Institute soon after its founding in 1950. By 1970, he was a Laboratory Chief at the Clinical Center, an editor of Science and the Review of Scientific Instruments, a successful physician-inventor, and a confirmed believer in the application of technology to diagnostic and therapeutic medicine. His student and coinvestigator, Theodor (“Ted”) Kolobow, M.D. (National Heart Institute, Bethesda, MD), became my teacher for the next 3 yr.

Ted was the inventor of a soup can–sized artificial lung. He joined the laboratory at NIH after his medical residency. When I met him in 1967, three decades before low tidal volume ventilation was proven beneficial for treating acute lung disease, Ted was convinced that mechanical ventilation was harmful to the acutely injured lung. He spent much of his effort developing artificial lungs in order to take the weight of gas transport off the injured natural lung so as to enable “lung rest.” Ted was (and is) brilliant and innovative,
with an extraordinary knowledge on the frontiers of plastics and polymers. He loved to fashion new kinds of tools for our research. He used his hands in our NIH workshop to craft novel membranes, catheters, and biocompatible surfaces.

I would like to share just one example. When we were faced with designing and making thin-walled, nonkinking catheters to drain aortic blood via the umbilical arteries of a sheep fetus (to develop and test an artificial placenta), Ted believed that stainless steel–reinforced polyurethane would be the ideal material for the catheter.7 E.I. du Pont de Nemours and Company (Wilmington, DE), which made Lycra®, stated they would have no part in providing the elastomer for our medical catheter. So, Ted dissolved a brassiere made from Lycra (taken surreptitiously from his home) and recast its polymer—reinforced with stainless steel wire—as a fetal umbilical catheter. It worked perfectly.

Perhaps most importantly for his young student, however, Ted was a true gentleman teacher. He never raised his voice, was accepting of a novice’s mistakes, and often let me learn by making errors and correcting the mistakes myself. He rarely spoke at meetings unless asked. “Don’t speak, publish” was his frequent counsel. Ted’s influence on my nascent research career was pivotal.

With the small hand-made, disposable, artificial lung at our disposal (0.2 M² surface area), the first problem that we set our sights on solving was infant respiratory distress syndrome. We chose a sheep fetus as the experimental subject because their birth weight (2.5–3.5 kg) is similar to that of newborn humans.

Few had explored this frontier before us—and none with the tools we possessed. All the members of the NHI team I organized turned out to be essential to our eventual success in isolated fetal perfusion.7 Ted led device development; he designed and hand-constructed membrane lungs from silicone rubber membranes cast for us at Dow Corning Corporation (Midland, MI). He also built a special nonocclusive blood pump head (to avoid blood damage),9 as well as the vital nonkinking thin-walled and flexible catheters. We recruited Gerald G. Vurek, PhD (NIH Clinical Center, Bethesda, MD),10 a bioengineer who designed a flow-thru oximeter for us; Joseph Pierce, DVM (NIH Clinical Center, Bethesda, MD), the NIH veterinarian who orchestrated our dated-pregnancy sheep and carried out the caesarian sections; and John L. Doppman, MD (1928–2000), Chief of Clinical Radiology, who helped us angiograph the circulation of fetuses supported on the artificial placenta—a study always performed late at night after patients had gone home (fig. 1).11

My first oral presentation at a scientific meeting was on the artificial placenta. It took place at the American Pediatric Society in Atlantic City, New Jersey. I had prepared carefully for the presentation, producing (with the assistance of the NIH Photography Branch) a 16-mm movie of isolated lamb perfusion in our dated-pregnancy sheep and carried out the caesarian sections; and John L. Doppman, MD (1928–2000), Chief of Clinical Radiology, who helped us angiograph the circulation of fetuses supported on the artificial placenta—a study always performed late at night after patients had gone home (fig. 1).11

Somehow, I made it through what seemed to be a successful presentation, complete with the movie. The New York Times and Life Magazine made appointments to follow the story. We wrote up our findings and published them in Science.6 Clearly, the world was ready for and fascinated by the possibility of using an artificial placenta to carry premature babies to term. Although that goal remains unrealized, after another three decades of advances by our group and many others,12,13 extracorporeal membrane lung perfusion of infants with the spiral coil artificial lung of Kolobow became a successful treatment for hypoxia of the newborn.

Another dream that we had was to use Ted’s artificial lung to help adults with acute lung injury. “Buying time with artificial lungs,” as Nikki poetically phrased it for the New England Journal of Medicine.14 This effort required another team of collaborators.

Although we performed the first perfusions with extracorporeal membrane oxygenation (ECMO) for adult respiratory distress syndrome (ARDS, as it was then known) at NIH, and for children with infant respiratory distress syndrome at the University of Puerto Rico (Río Piedras) and at Children’s National Medical Center (Washington, D.C.), I became convinced that, for me, leaving the sheltered halls of NIH for full-time clinical training would be necessary. I wanted to be certain ECMO was a better treatment for acute respiratory distress syndrome than standard mechanical ventilation. Ralph A. Epstein, MD, then an anesthesiologist at the NIH Clinical Center (later Chief of Anesthesiology, University of Connecticut, Farmington), steered me toward a residency in anesthesiology and an interview with Richard J. (“Dick”) Kitz, M.D., who had just been selected to follow Henry “Harry” K. Beecher, MD (1904–1976) as Chief of Anesthesia at Massachusetts General Hospital (MGH) in 1969.
MGH Pioneering

Team 2: ECMO for ARDS

My interview with Dick was the clincher. He assured me of his support for my career as a clinical investigator; introduced me to Henning Pontoppidan, M.D., and Myron B. ("Mike") Laver, M.D. (1926–1982), who were on the frontiers of mechanical ventilation and oxygen transport, respectively; and suggested that I write an R01 grant titled "ECMO for Acute Respiratory Failure" with Dick as the primary investigator.

The grant was to be an initial test of ECMO in the laboratory and on ARDS patients. Dick then fashioned a way for me to continue my life at the frontiers of respiratory research while completing my residency. It was an offer I could not refuse. He suggested as our coinvestigators W. Gerald ("Jerry") Austen, M.D., and Mortimer ("Mort") Buckley, M.D. (1932–2007), MGH chiefs of surgery and cardiac surgery, respectively. We also had Henning and Mike as respiratory and cardiovascular coinvestigators. Realizing that I was going to be the one to do the long and grueling initial large animal and human perfusions, Dick kindly offered me a slightly longer anesthesiology residency (then 24 months) with each Friday reserved for ECMO perfusions in large animals (cows and sheep), and time off from the residency for human ECMO trials, which might last, as we later learned, up to 3 weeks (fig. 2).

Exploration of the human ECMO frontier at MGH lasted more than 8 yr, well beyond my residency. The work led to a national, multicenter prospective and randomized trial of the technique.15

At the start, we had to build a team and learn the basics of ECMO. Which way should we hook up the ECMO device to the patient? Arteriovenous (draining blood from an artery and returning to a vein like the fetal perfusion), venoarterial (like cardiopulmonary bypass), or venovenous (draining from a vein and returning to a more central vein)? The answer wasn’t obvious when we began, and only slowly over several years did we learn that venovenous was the preferred route in respiratory failure because it did not reduce cardiac output. Other burning questions arose. How much anticoagulation was necessary? Which diseases might respond to ECMO therapy? How long should ECMO therapy be continued? How best to treat the natural lung while receiving ECMO therapy? The list of questions was quite long and growing.

In addition to Pontoppidan and Laver in respiratory and cardiovascular physiology, we were joined by two anesthesiology residents, Michael T. Snider, M.D., Ph.D., who remained on staff and helped us understand the physiology of bypass and pulmonary circulation,16 and Robert C. "Bob" Schneider, M.D., who examined the profound thrombocytopenia of bypass.17,18 We recruited Angelina Carvalho, M.D., from Hematology at MGH, to help us understand the frontiers of ARDS/ECMO-induced coagulopathy.18 Realizing that progressive pulmonary fibrosis was the outcome of severe ARDS, we recruited Robert L. Trelstad, M.D. (1940–2010), a pathologist at MGH who was studying the molecular biology of connective tissue.19

Pontoppidan’s immense and encyclopedic understanding of respiratory physiology inspired the studies of positive end expiratory pressure (PEEP) by Konrad J. Falke, M.D.,20 who was also then at MGH (later Chief of Anesthesiology, Freie Universität, Berlin, Germany). After the pioneering PEEP report of Ashbaugh et al.,21 the MGH studies led to widespread use of PEEP to augment arterial oxygenation, increasing our understanding of its mechanism of action.

Laver, ever the insightful genius, contributed to our efforts in many ways, but in my mind, mostly by making critical statements like “PEEP can get a decent PO2 … from a liver, don’t confuse PEEP with an improved status of the lung.” He also motivated us in our examination of pulmonary vascular resistance. One day during a long ECMO run, we were trying to save the life of an 18-yr-old girl with an aspiration pneumonia and amniotic fluid embolism. Laver asked me what her pulmonary vascular resistance value was. I reported 7 or 8 Wood units. He looked me in the eye and said, depressingly, “Give up. Go home. You will never cure her.”

His insight into the importance of destruction of the pulmonary vasculature in ARDS, a heretofore unexplored area, led me to a decade of studies. Of course, this circulatory frontiersman was quite correct—and although crushing our hopes for the survival of our young patient—Mike led us to a decade of productive studies on the acutely injured pulmonary circulation and its effect on the right ventricle.22

In-depth pulmonary studies required expanding our team to include the inimitable Lynne Reid, M.D., M.B.B.S., newly recruited from the United Kingdom to Children’s Hospital Boston as Chair of Pathology. Lynne was a renowned Australian pulmonary vascular pathologist and, assisted by her colleague Rosemary Jones, Ph.D., helped us cast and measure the major destructive vascular changes of the human lung in ARDS.23 We...
also recruited Reginald Greene, M.D., a radiologist at MGH, to image the pulmonary circulation of ARDS patients in their intensive care unit beds with a simple static image by using their Swan-Ganz catheter, a technique he popularized and named “balloon occlusion pulmonary arteriography.”

The extension of our studies into the basics of pathology and imaging the pulmonary circulation merited further support, and we received funding for a decade as an NIH-sponsored Specialized Center of Research in ARDS (1978 – 1988). Our laboratory, our clinical studies on ECMO, and our subsequent researches on ARDS attracted the finest clinicians from near and far to our work. ECMO was complex, the patients young and often doomed by ARDS, and our therapy was radically different. Jesper Qvist, M.D., of Copenhagen, and Falke were research fellows. Fascinated by ECMO, they subsequently took the technique back to Europe with them. Falke eventually developed the finest German intensive care unit specializing in ECMO. Qvist organized and sponsored a pivotal research meeting on ECMO at Rungstedgaard, Denmark, in June 1975. This well-attended meeting and the book that followed placed ECMO research on the international map of frontiers to be explored.

Team 3: Studying the Weddell Seal of Antarctica

While spending days and weeks on ECMO, we would often speak of other important areas of respiratory research. Perhaps the most exciting and unexplored area was the tolerance to hypoxia exhibited by habitually diving marine mammals. Qvist and I began reading a report of a symposium held at the December 1968 American Association for the Advancement of Science meeting in Dallas, TX. It described research by Gerald Kooyman, Ph.D., of University of California, San Diego, on Weddell seals (Leptonychotes weddelli) and Arthur L. DeVries, Ph.D., (University of Illinois, Urbana, IL), then of University of California, San Diego, on the Antarctic codfish (Dissostichus mawsoni). The Weddell seal is large (350–450 kg, 6-foot long) and takes hour-long dives to 500 m in the icy waters off McMurdo Station, Antarctica. The Antarctic codfish lives in near −2°C seawater and produces a glycoprotein antifreeze to keep its blood and other body fluids from freezing. In comparison, the human tolerates deep hypothermia poorly, with breath-holds of 4 min breathing air being close to our physiologic limit. How did seals tolerate this hypoxic exposure? What physiologic and biochemical strategies had they evolved? Could any of this knowledge be used in treating human respiratory failure?

George Llano, Ph.D. (1910–2003), at the National Science Foundation (Arlington, VA) was enthusiastic and supportive of our interest, and he enabled us to travel to Antarctica (the “Ice”) via U.S. Navy aircraft and spent a month on the sea edge, at 78°S (800 miles from the South Pole). McMurdo was a wonderland on the shores of Ross Island, an active, 12,448-foot high volcano covered with ice, snow, and glaciers, surrounded by exotic fish, mammals, and birds—most of them as yet unstudied with modern physiologic and biochemical methods (fig. 3).

To enter this exotic and isolated icy world, where austral spring temperatures in October hovered at approximately −18°C (and occasionally dropped to −30 to 40°C), we had to learn to work safely on sea ice—which was beginning to melt and break up in storms and drift north in the Antarctic spring to join the circumpolar pack ice. Our only communications with home were via ham radio patches (I am licensed as W1GWN) from our amateur radio in Antarctica.

Thus began a series of eight expeditions, supported by grants from the U.S. National Science Foundation, which enabled us to revolutionize our understanding of marine mammal diving. I collected a group of experts to explore this southern frontier of science (figs. 4 and 5). Peter Hochachka,
Ph.D. (1937–2002; Professor of Biochemistry, University of British Columbia, Vancouver, Canada), was the foremost comparative biochemist of the era and joined our group a half-dozen times, sampling and studying seals at McMurdo with his fellows, Brian Murphy, Ph.D., Michael Guppy, Ph.D., and Maggie Castellini, Ph.D. Sir Graham C. ("Mont") Liggins, M.D., Ph.D. (1926–2010), of Auckland, New Zealand, joined us to explore the physiology of fetal seals, the "submarine inside of the submarine." Mont became a fellow of the Royal Society of London for the Improvement of Natural Knowledge and was dubbed "Sir Mont" after being knighted for his discovery of the importance of cortisol-inducing maturation of the surfactant system of the premature lung and first to show its effects in humans.

Falke and Qvist focused on measuring nitrogen and respiratory gas concentrations in seal blood, respectively. Bob was our skillful seal anesthesiologist and physiologist; he organized and provided anesthesia and surgery. And perhaps most foresightedly, at the beginning of the microprocessor age in 1979, I recruited Roger D. Hill, D.Phil., a physicist and recent Oxford graduate who was then a pulmonary circulation research fellow in my MGH laboratory, to take on a most revolutionary task (figs. 6 and 7). Roger designed, developed, and programmed a diving microcomputer (56 KB random-access memory) that was capable of recording physiologic data (e.g., electrocardiogram, body temperature, seawater depth, velocity) and commanding a pump to draw blood samples while submerged.

The team’s choreography for the seal experiments was loosely scripted and always an adventure. A seal weighing 600 pounds basking on the sea ice at 0°C has a mind of its own. First, we had to capture it by placing a bag, with a breathing hole, over its face. Many of our team sustained lasting bruises from this seemingly simple operation. Although the seals were surprisingly agile on the slippery sea ice, we generally were not. Then, Liggins had to perform a vaginal examination on the awake seal to determine pregnancy—another trial on sea ice. Several times, those of us holding the rear flippers to steady the seal feared that Mont would experience a traumatic arm amputation when the seal realized what this human was attempting and reacted with a quick 180° roll. Taking off one’s white coat and slipping on a glove greased with lubricant jelly to perform a pelvic examination is not a problem in most obstetricians’ warm offices. But, removing an insulated coat in Antarctica at −40°C in a 20-knot breeze to perform a phocid pelvic examination is an entirely different story.

After a few such chilly examinations, Mont, ever inventive, designed a special Antarctic obstetrician’s coat. He cus-
tomized one of our standard well-insulated red overcoats by cutting off the right sleeve at the shoulder and rehitching it with Velcro for easy removal. At his next phocid field pelvic examination, Mont speedily removed the sleeve, pulled on his long glove and … Presto! He proceeded with the pelvic examination, his body remaining warm while his arm probed the warmth, seeking the fetal head. One of our French colleagues gave this inventive Antarctic coat a fancy moniker: “la manche de l’accoucheur” (roughly translated as “the obstetrician’s sleeve”). And, thus, it became known that year throughout Antarctica. Although Mont had made himself more comfortable with his ingenious costume, by the second season working on the ice, he had worked out that, by obtaining epidural vein blood samples from all the tagged female seals and measuring plasma progesterone, he could determine pregnancy in the heated laboratory at McMurdo. We abandoned the hazards of performing phocid vaginal examinations on the ice.

The selected seal was coaxed into a sled, then hauled to our isolated ice hole where it was sedated with a brief, short-acting anesthetic (1 g intramuscular ketamine), followed by a brief general halothane anesthetic with a to-and-fro system, a 25-l reservoir bag and a carbon dioxide absorber. The seal was soon ready for its electronic fitting. We attached Roger’s sampler by gluing it to the seal’s fur. It was capable of taking several samples of arterial blood at various programmed depths and times from a free-swimming Weddell seal. The seal was released to dive beneath the fast ice from an isolated off-shore hole that we drilled thru the ice sheet. We retrieved the data when the seal returned to our hole to breathe while briefly connected via a fiber optic cable to the field laboratory computer (fig. 7).

At that time, there was a growing belief that there was no such thing as a “diving reflex,” the profound circulatory redistribution brought about by selective systemic vasoconstriction and vagal bradycardia that first had been observed in captive diving animals and birds and described as “the master switch of life” by the Norwegian-American physiologist Per F. Scholander, Ph.D. (1905–1980).29 There were publications reporting that prior observations of bradycardia were the effect of handling and fear in diving animals, and that, in the wild, bradycardia did not occur.30,31 Roger’s computer would be the best test of the hypothesis because it would be placed on awake and free-diving Weddell seals in their natural habitat.

In the course of two Antarctic spring field seasons near McMurdo, we set modern diving physiology on the map.32 The microcomputer monitor worked splendidly, recording prompt diving bradycardia at the start of each dive, showing the “diving reflex” indeed operated in free-diving seals setting forth at will to catch fish at 200–300 meters beneath the sea ice.33 An intense diving bradycardia remained present for the entire duration of the dive, until the seal again breathed at the surface. Scholander’s hypothesis was verified. Perhaps more remarkably, we were able to obtain several blood samples during each dive. Qvist made measurements documenting that, on each dive, the seal’s arterial PO2 fell to 20–30 mmHg, a concentration often lower than that estimated from exhaled gas samples obtained from humans summiting Mount Everest (28 mmHg).34,35 Thus, the Weddell seal was capable of tolerating levels of hypoxia on every dive that would cause a terrestrial mammal or human to lose consciousness.

Another riddle was solved with our diving computer. Master physiologist Hermann Rahn, Ph.D. (1912–1990), Chairman of the Physiology Department, University of Buffalo, New York, taught Falke to measure blood nitrogen content with an old but reliable instrument, the Van Slyke apparatus.36 Falke was able to measure the nitrogen content of the arterial blood samples drawn as the seal descended and ascended the water column (fig. 8). He found that blood nitrogen concentrations in the seal’s blood ascended 3–4 times those at the surface, equivalent to approximately 30 meters of seawater pressure.37 Thereafter, during the dive, blood nitrogen concentrations stopped ascending and began descending slowly. These painstaking measurements made in a drafty field hut on the sea ice, 20 miles offshore, confirmed the hypothesis that the seal’s lung completely collapses on each dive below depths of 25–50 m, thus ceasing the uptake of nitrogen from alveolar gas into the blood. The seal’s lung then becomes airless, like the lung of a fetus. And perhaps even more surprising, we measured an increased concentration of nitrogen in the blood on surfacing at the end of the dive. Thus the seal’s blood remained “supersatu-

Fig. 8. Konrad J. Falke, M.D., measures blood nitrogen concentrations of seal with Van Slyke apparatus in field laboratory hut.
rated” with dissolved nitrogen after each deep dive. This insight has given us an understanding of why marine mammals are so sensitive to developing the bends when their diving patterns are disturbed by naval sonar. Other startling discoveries of our Antarctic studies were made by William E. Hurford, M.D. (Professor and Chairman of Anesthesiology, University of Cincinnati, Ohio), who used ultrasound to measure spleen size before and after diving (fig. 9). He found the diving reflex extends to the spleen. After a seal rested in the hole and commenced a dive, its spleen discharged approximately 20 liters packed red cells into circulation, thus giving the seal added circulating red cells to rapidly take up oxygen while it briefly breathes at the surface during a series of dives.

In our last scientific expedition to Antarctica, Gregory Guyton, M.D., then a Harvard medical student and youngest son of the legendary physiologist, built and tested a diving oximeter to measure the rate of deoxygenation of the Weddell seal’s swimming muscle (combined desaturation of hemoglobin and myoglobin). The reason for the intense black color of seal and whale meat is the rich myoglobin concentration. Guyton found that the Weddell seal’s myoglobin slowly desaturates (2.5% per min) during long free dives (more than 17 min). He further determined that the enormous oxygen stores held by the seal’s muscles are slowly released during diving.

My son, David, then a junior at Massachusetts Institute of Technology (Cambridge, MA), set up our field laboratory for that expedition and served as a laboratory technician. He did remarkably well setting up our field camp at the Stranded Moraines, approximately 35 miles west of McMurdo, 25 miles from our nearest neighbor, a fish physiologist in Fish Hut No. 5. In the course of our busy field work schedule, I began to notice that David wasn’t always around when we needed his assistance.

Eventually, Bob tattled. David was on a “date.” “Where did he find a date on this ice sheet?” I replied incredulously.

The story is now part of family legend, as Diana Laird, Ph.D., a remarkable young budding scientist, was our Fish Hut No. 5 neighbor—and David’s splendid future wife. Their first child, Ruth Karoline Zapol, was born a decade later, in 2004, and bears the name of Karoline Mikkelson, the first woman to step foot on the continent of Antarctica (fig. 10).

I have, in fact, “infected” my entire family with the Antarctic bug. Nikki, as well as my daughter, Liza, have accompanied me in leading tourists to Antarctica for the Harvard Museum of Natural History. In 2006, I was surprised to learn that a glacier in Antarctica had been named after me by the U.S. Board on Geographic Names (fig. 11). The Zapol Glacier (78°S, 85°W) is, in my opinion, named for our entire Antarctic research team and its many discoveries.

Although there was little of immediate value to be brought back to the hospital to help us save human lives in the MGH intensive care unit, these many other exciting and productive Antarctic seal studies gave us great insights into mammalian adaptations for diving.

**Team 4: Inhaled Nitric Oxide to Treat Persistent Pulmonary Hypertension of the Newborn**

In contrast to our Weddell seal studies, our work with inhaled nitric oxide would change the therapy of newborn respiratory failure. By 1988, I had studied pulmonary circulation for two decades, and I was convinced that the high pulmonary vascular resistance of adults with ARDS and...
hypoxic newborns had to be reduced to reverse hypoxia and enhance survival. But how to do it safely?

For a decade, Michael T. Snider, M.D., Ph.D., and I had studied pulmonary vasodilators with intravenous infusions of nitroprusside (later known as a nitric oxide donor compound) and isoproterenol. Both drugs produced nonselective systemic and pulmonary vasodilation, dilating vessels in the shunting-injured areas of the ARDS lung and lowering arterial oxygen concentrations. Our attempts to lower pulmonary artery pressure were stymied by the hypoxia these drugs produced. I was also particularly impressed by an early research study wherein a child with end-stage chronic pulmonary artery hypertension was treated with a new vasodilator, intravenous prostacyclin. As the prostacyclin dose was increased, her pulmonary artery pressure diminished but her systemic pressure was also reduced. She went into shock and suffered a cardiac arrest. Unfortunately, her physicians were unable to resuscitate her. That sad experience taught me that intravenous infusion of vasodilator drugs is a dangerous way to treat pulmonary artery hypertension, and it motivated me to seek another route to dilate lung vessels selectively without producing hypotension.

In 1986, there was great excitement when nitric oxide, a small, evanescent and overlooked molecule was determined to be the active ingredient of endothelium-derived relaxing factor. Rapidly, it was learned that nitric oxide was produced by endothelial cells and was a potent dilator of pulmonary and systemic vascular smooth muscle. It was the key and previously unknown ingredient released by nitroprusside and nitroglycerin, a discovery that ultimately, in 1998, led to the Nobel Prize in Medicine being awarded to Louis J. Ignarro, Ph.D., Robert F. Furchgott, Ph.D. (1916–2009), and Ferid Murad, M.D., Ph.D. I was fascinated by this extraordinary gas and began laboratory studies with my fellow, Claes Frostell, M.D., Ph.D., of the Karolinska Institute, Solna Sweden (now Chairman of Anesthesiology there). Nitric oxide was known at that time to be a pollutant and toxic gas, rapidly converted to nitrogen dioxide which then dissolved in water, producing nitric acid. Many had been killed by inhaling nitric oxide gas (Silo filler disease, anesthetic poisonings with nitrous oxide contaminated by nitric oxide).

Our first sheep study, done wearing gas masks and with the laboratory windows wide open to avoid poisoning the experimenters, showed that breathing low doses of nitric oxide could reverse chemically produced pulmonary vasoconstriction without producing systemic vasodilation in an awake lamb (fig. 12). The onset of selective pulmonary vasodilation was within seconds of inhaling the gas, and the offset was equally rapid. The results were clear and unequivocal. I rapidly assembled a team to learn how nitric oxide worked, if it was safe, and what respiratory diseases it could be used to cure or treat.

The team consisted of Jesse (“Jay”) D. Roberts, M.D., who had just completed the MGH Anesthesiology Chief Residency and was also a trained neonatologist. Jay examined the effects of inhaled nitric oxide in fetal sheep and then treated human infants with hypoxia and persistent pulmonary hypertension of the newborn. David M. Polaner, M.D., a pediatric anesthesiologist (now Professor of Anesthesiology and Pediatrics, University of Colorado, Aurora, CO), joined Jay in the studies of the newborn. Jay also studied children with congenital heart disease, demonstrating that their pulmonary vessels were also selectively dilated by inhaling nitric oxide.

Kenneth D. (“Ken”) Bloch, M.D., of MGH Cardiology (now William Thomas Green Morton Professor of Anesthesia at Harvard) was introduced to me in 1990 by my wife Nikki who was then working in the MGH Office of Technology Transfer. Ken had elucidated the sequence of the gene...
coding for endothelial nitric oxide synthase and had contacted her office. Using his remarkable skills in molecular biology, Ken collaborated with us in examining the mechanisms of the interaction of inhaled nitric oxide with nitric oxide synthase isoforms in healthy and injured lungs. He was able to measure the expression of the enzyme soluble guanylate cyclase, the receptor for nitric oxide, in lung tissue during fetal development, as well as plasma concentrations of cyclic guanosine monophosphate, the messenger product of soluble guanylate cyclase. We learned that cyclic guanosine monophosphate is produced in large quantities by the lung when inhaling nitric oxide. We were surprised to find there was an arteriovenous difference (a step-up) of plasma cyclic guanosine monophosphate concentrations across the lung when breathing nitrous oxide. For me, this was the beginning of a long and close friendship and productive scientific collaboration with Ken that led us much later, in 2008, to physically join our research laboratories.

Fumito Ichinose, M.D., Ph.D., sent to the MGH anesthesia residency program by Shigeho Morita, M.D. (1948–2010), of Tokyo, joined me as a fellow examining the pathways of cyclic guanosine monophosphate breakdown by phosphodiesterase, and their inhibition by phosphodiesterase-5 inhibitors like sildenafil. Luca Bigatello, M.D., a recent addition from Milan, Italy, worked with Hurford and began studying the effects of inhaled nitrous oxide in ARDS patients. Falke, working with fellow Rolf Rossaint, M.D. (now Chief of Anesthesiology, Aachen University, Aachen, Germany), has also studied inhaled nitric oxide in ARDS patients in Berlin. They published their remarkable observations that inhaled nitric oxide selectively dilated the injured lung and decreased the amount of blood shunting through the ARDS lung. However, this brief summary only begins to describe the effects of nitric oxide breathing our team studied. Within a short span of 3 yr, the scientific world had changed from viewing nitric oxide as a toxic pollutant to considering it as a therapeutic gas with remarkable properties and a safely inhaled therapeutic agent that can be used to reverse pulmonary hypertension.

Jumping ahead two decades, our team’s clinical studies of inhaled nitric oxide, as well as the studies of many others, led to several successful randomized trials of inhaled nitric oxide therapy for children with persistent pulmonary hypertension of the newborn as well as other causes of hypoxic respiratory failure of the newborn. Those studies demonstrated that inhaled nitric oxide led to a reduction of the use of ECMO, as well as an increase in survival of these children, and led to approval by the U.S. Food and Drug Administration in December 1999 for the use of inhaled nitric oxide to treat newborns at term gestation with hypoxic respiratory failure. In subsequent years, the use of inhaled nitric oxide has become widespread, with 30,000 children and adult patients treated with the drug each year in the United States. Its primary uses are in infants with persistent pulmonary hypertension of the newborn and hypoxic respiratory failure, although it is widely used during and after cardiac surgery in children based on the pioneering studies of David Wessel, M.D., and his colleagues at Children’s Hospital Boston, as well as during left ventricular assist device implantation in adults. At this time, we estimate that a total of 360,000 Americans have been treated with inhaled nitric oxide for pulmonary hypertension. It is surprising perhaps that there are very few reported complications. Inhaled nitric oxide, as currently used, is a very safe therapeutic intervention.

Teambuilding

Teambuilding is the essence of modern medical advances. The days of a lone inventor making a solo invention that alters clinical medical therapy are over. A paradigm-shifting therapeutic invention, such as inhaled nitric oxide, requires a talented group of medical collaborators—anesthetists, intensivists, pediatricians, neonatologists, cardiologists, and surgeons—who can fuse their work with a group of laboratory scientists. The latter group includes physiologists, molecular biologists, biochemists, organic and inorganic chemists, developmental biologists, toxicologists, pathologists, and statisticians. They propel the laboratory and clinical science, moving it down the road toward useful pharmacologic advances.

But, to actually turn inhaled nitric oxide into an approved drug took the cooperation and investment of hundreds of millions of dollars by industry. The MGH Office of Technology Transfer deserves great credit for its teamwork in getting industry to license our technology. First, inhaled nitric oxide had to be patented. Janis K. Fraser, Ph.D., J.D. (Fish & Richardson, Boston, MA), has been the hospital’s superb patent lawyer on this invention, working for two decades on inhaled nitric oxide. Because the commercial gas industry, which we needed to produce nitric oxide, is known neither for scientific advances nor for experience with drug development, Charlotte Harrison, J.D., and Marv Guthrie, J.D., in the MGH Technology Transfer Office put enormous effort into helping us convince industry and work out licensing agreements. Eventually, we were able to motivate two business champions to save the lives of blue babies by devoting a decade to advancing inhaled nitric oxide into product approved by the U.S. Food and Drug Administration. These individuals are Ashleigh Palmer, M.B.A., at Ohmeda (then a division of the British Oxygen Corporation) and Rolf Petersen, M.B.A., at AGA (then a Swedish gas company). Eventually the British Oxygen Corporation and AGA became subsidiaries of Linde AG (Munich, Germany), which later sold its commercial rights to Ikaria, Inc. (Clifton, New Jersey).

Bringing inhaled nitric oxide from a laboratory invention to a commercially useful product involved the largest team effort that I ever belonged to. Its success depended on each person contributing his or her best efforts. Many of our nitric oxide team efforts succeeded, and, I imagine, that is why I am here today writing this story. But, it is also important to note that some of our studies have not yet given positive results.
Because nitric oxide signaling contributes to so many pathophysiologic pathways, research never seems to end on inhaled nitric oxide. A number of other applications of inhaled nitric oxide are in active clinical trials around the world. These studies include the adjunctive treatment of cerebral malaria, the prevention of chronic lung disease in premature infants, and reducing the size of myocardial infarcts after reperfusion.

My collaborative research group with Kenneth D. Bloch, M.D., now numbers approximately 25 physicians and scientists and fills an entire floor of laboratories. Figure 13 shows our lively team in front of the MGH Bulfinch Building (Boston) and its Ether Dome, a historic place where, in 1846, the demonstration of another inhaled gas, ether, played an important role in medical history. Part of our team is working on hemoglobin, which is toxic when released by hemolysis of red cells or when given as an artificial oxygen-carrying substance, in part as a result of its avid scavenging of nitric oxide. Although I am confident that there will never be a nitric oxide dome at MGH, our laboratory team members are hoping that, one day in the future, another drug invented and tested in the shadows of this building will again alter the practice of medicine.

Finally, I hope my story encourages others to seek and take advantage of the power of teamwork in making contributions to science and medicine. I can assure you that doing so is a near-guarantee of a most gratifying life at your own frontier.

This article is dedicated to the memory of Sir Graham C. (“Mont”) Liggins, M.D., M.B. Ch.B. (1926–2010), Professor of Obstetrics and Gynecology, University of Auckland, New Zealand, of the Antarctic research team. He was an important friend and mentor.

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