THE FACULTY OF MEDICINE
Harvard University

Warren Myron Zapol

Warren Myron Zapol, M.D., visionary, inventor, polar explorer, Massachusetts General Hospital critical care physician and anesthesiologist, mentor, colleague, friend, and beloved husband, father and grandfather, died December 14, 2021. To his last day, the Reginald Jenney Distinguished Professor of Anesthesia at Harvard Medical School challenged those around him to think bigger — far outside the box — about lung and cardiovascular physiology. His insights about how lung physiology is altered by extreme conditions and disease led to his discovery of a life-saving therapy that continues to be used in critically ill patients of all ages throughout the world.

Born in Brooklyn, NY, on March 16, 1942, Warren learned decades later that he was adopted by neighbors at birth, following the death of his mother from eclampsia. Bernard Zapol, a businessman, and his wife, Florence, a schoolteacher, nurtured Warren as their own, steered him to Stuyvesant High School in Manhattan, and sent him off to the Massachusetts Institute of Technology at the young age of 16. There, he studied biology and spent a great deal of time in the amateur radio club; he was an avid ham his entire life (W1GWN). Warren skipped his 1962 MIT graduation ceremony to lead a group of classmates on an overland scientific goodwill expedition by Land Rover to Southeast Asia. During the trip, he contracted malaria and became extremely ill. Saved – and inspired – by a Harvard Medical School-trained nurse-nun in Rawalpindi, Pakistan, Warren set his sights on becoming a doctor.

Warren returned to the United States, enrolled in the Boston University School of Medicine, and then transferred to, and graduated from, the University of Rochester School of Medicine. Following an internship on the Harvard Medical School surgical service at Boston City Hospital, he was accepted into the Public Health Service as a research associate in a laboratory led by Dr. Theodor Kolobow at the National Institutes of Health (NIH). Using hand-made, silicone rubber membrane "artificial lungs," Warren

In tribute to their dedicated efforts to science and medicine, deceased members of the Harvard Faculty of Medicine (those at the rank of full or emeritus professor) receive a review of their life and contributions with a complete reflection, ***a Memorial Minute****.*

and Ted conducted animal and human studies of extracorporeal membrane oxygenation (ECMO), a temporary, life-sustaining means of oxygenating the blood outside the body while giving lungs time to heal. Warren responded promptly when the U.S. military requested that he try ECMO on wounded soldiers in Vietnam, a futile yet eye-opening effort given the extent of their bodily injuries. One far-sighted demonstration of this exciting technology was its use as an artificial placenta that kept a fetal lamb alive while it was submerged in an aquarium tank filled with synthetic amniotic fluid.

After completing his research at the NIH, Warren applied to several residencies. Dr. Richard J. Kitz, then chief of the MGH Department of Anesthesia, offered Warren an anesthesia residency combined with support and protected time for research during his training. The draw was compelling: MGH had the first respiratory care unit in the nation, established by Dr. Henning Pontoppidan, and it had a premier blood-gas laboratory led by Dr. Myron Laver. For the next 52 years, Warren remained tethered to the MGH as a clinician, researcher, and, from 1994 to 2008, its third Anesthetist-in-Chief.

Warren's many contributions toward improving clinical care and science at MGH were marked by his enduring belief in the importance of teamwork and the value of every team member's contribution. He had the keen ability to assemble teams of clinicians and investigators to enact his vision. His early efforts with Drs. Patricia Donohoe and John Ryan, for example, led to the creation of a surgery-anesthesia team that provided ECMO for critically ill newborns. During his time as Anesthetist-in-Chief, the MGH Department of Anesthesia achieved remarkable growth in the number of patients, staff, and trainees as well as significant expansion of the breadth and scope of the service and increased research funding. Importantly, the Anesthesia and Critical Care Service assumed more of a leadership role in the oversight of the operating rooms. Warren championed the ongoing quest to raise anesthesia safety and ardently supported the use of clinical simulation training as a vital – and safer – technology for learning, practicing, and polishing clinical skills. He encouraged an entrepreneurial spirit, supporting such wide-ranging efforts as developing smart IV pumps, improving monitors, and using a computerized intraoperative record system. He brought acupuncture services and research into the department. He made pain medicine an investigative priority and supported ongoing studies seeking to unravel the mysteries of the brain under anesthesia. In addition, he established four Harvard Medical School-endowed chairs in anesthesia at MGH, supporting the research careers of several investigators in the department.

One of Warren's crowning achievements for medicine – and humanity – was his pioneering work with nitric oxide (NO). Nitrogen oxides, including NO, were known to be gaseous components of air pollution. But work by others had demonstrated that NO produced within the body also serves as a signaling gas in the cardiovascular system. Warren was fond of telling the story of how a newspaper article about nitrogen oxides in air pollution prompted him to wonder whether inhaling low levels of purified NO could actually be therapeutic. Pharmacologist Lou Ignarro, one of three scientists to receive the 1998 Nobel Prize for discovering NO's signaling activities, said he initially had doubts about Warren's unorthodox idea of NO inhalation because of NO's potentially toxic properties. During successful bench-to-bed experiments, initially involving designing and constructing a safe NO

inhalation system and newborn lambs, Warren and Dr. Jesse Roberts Jr., an MGH neonatologist and pediatric anesthesiologist, were the first to demonstrate that inhaled NO could safely treat "blue babies" – the color signifying a failure in oxygenation. In the pioneering studies in the MGH intensive care nursery, critically ill blue babies turned pink right before the eyes of the eager and ecstatic caregiving team. These clinical observations were first reported in *Circulation* in 1991. A landmark *Lancet* paper was published a year later, establishing inhaled NO as an effective and safe treatment for persistent pulmonary hypertension in the newborn. Their work, joined by others entering the field, led to FDA approval of inhaled NO in 1999 for the treatment of critically ill blue babies. Subsequently, inhaled NO was administered to patients of all ages with cardiovascular-related complications. Today, more than 10,000 patients a year receive inhaled NO. In recognition of this groundbreaking work, in 2003, Warren received the Inventor of the Year Award from the Intellectual Property Owners Association.

Beyond NO, Warren earned a reputation as a bold explorer, earning him the moniker "Dr. Adventure." Beginning in 1974, he led a series of nine expeditions to Antarctica to study the physiology of Weddell seals, marine mammals that dive more than 600 feet below the surface of the ice where they can remain for more than an hour while avoiding the bends and maintaining adequate oxygen levels. His team devised bespoke microcomputer-controlled sensors, which were temporarily glued on the seal's fur to capture real-time vital signs and blood samples during diving. These seal studies shed important light on physiologic mechanisms of adaptation. Warren's commitment and contributions to Antarctic science prompted the US Board of Geographic Names to honor him in 2006 with his own glacier. The Zapol Glacier extends from the west side of Mount Vinson, the highest peak at the bottom of the world. In addition, Warren led an international team of scientists to South Korea to study the respiratory physiology of the ama, deep-diving women who forage the ocean floor for abalone. This work fostered a new understanding of the role of the human spleen as a built-in scuba tank, releasing oxygenated red blood cells during dives. This work in extreme environments led President George W. Bush to select Warren in 2008 to serve on the U.S. Arctic Research Commission; he was reappointed to that group in 2012 by President Barack Obama. His scientific achievements near and far earned him membership in the National Academy of Medicine. He was named to the Polar Research Board at the National Academies of Sciences, Engineering, and Medicine, and served as chair of its Committee on Future Science Opportunities in Antarctica and the Southern Ocean, which published its comprehensive report in 2011.

Warren drew his whole family into his fascinating orbit. Nikki, his wife of 53 years, served in both the technology transfer and legal offices at MGH and Partners HealthCare and joined Warren to lecture on Harvard-organized cruise expeditions to the Antarctic. Their son, David, was a member of one of Warren's early Antarctic research expeditions, met his future wife there, and later became the first CEO of Third Pole, Inc., a company formed to develop another Zapol invention, a novel device that generates NO gas using an electric spark from air. Warren's daughter, Elisabeth (Liza), joined Warren on an adventure-filled ice-breaker cruise to McMurdo Station in Antarctica. Three grandchildren, Ruthie and Elliot Zapol, and Juno Townsend, have imbibed Warren's infectious and far-ranging spirit.

Perhaps Warren's greatest legacy – beyond pioneering therapies and opening scientific pathways – can be found in the life-changing personal connections he forged with the generations of people who trained with, learned from, and were inspired by him. As department chief, Warren insisted on interviewing every resident applicant, often challenging them to identify the eclectic assortment of skeletal bones perched on shelves in his office. He was a mesmerizing lecturer and raconteur. He was an inspirational leader, with a unique talent for leading from behind, encouraging all who came within his strong gravity field to pursue their own scientific and medical interests and instincts. His infectious, boyish, good humor, twinkling eye, and can-do optimism permeated his ever-expanding orbit. Generations of leaders in anesthesia around the world trained under him. As a faculty member of the Harvard-MIT Health Sciences and Technology program, he was particularly noted for his enthusiasm in introducing MIT graduate students to clinical and translational research. His influence even extended into space, as his fellow Jessica Meir became a NASA astronaut and carried the MGH flag to the International Space Station in 2020. The MGH Anesthesia Center for Critical Care Research, which he established together with Dr. Kenneth Bloch, in part with royalties the MGH received from the sale of nitric oxide, continues to advance this game-changing science while inspiring young investigators. Until his own final breath, this happy warrior, though stringent in his expectations, shed a brilliant light on their future and made their work fun.

Respectfully submitted,

Lorenzo Berra, *Chairperson*
Emery N. Brown
Patricia K. Donahoe
Fumito Ichinose
Louis Ignarro
Edward Lowenstein
Jesse D. Roberts
Vamsi K. Mootha
Nikki J. Zapol