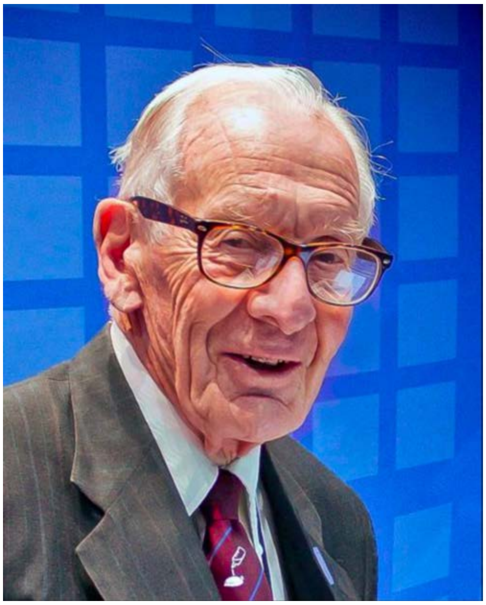
John W. Severinghaus, M.D., 1922 to 2021

Philip E. Bickler, M.D., Ph.D., Thomas Hornbein, M.D., Lawrence J. Saidman, M.D.

John W. Severinghaus, M.D., who invented modern blood-gas analysis by combining electrodes for carbon dioxide, oxygen, and pH into one machine, died June 2 at age 99. He was also the first to measure the uptake of inhaled anesthetics in the lung, developed methods for measuring end-tidal gases in the operating room, and was a major figure in studying the control of breathing and adaptation to high altitude in humans. John truly was among the important thought leaders in anesthesiology in the last century and was honored as the first recipient of the American Society of Anesthesiologists award for research in 1986. Born the same year that J. S. Haldane's *Respiration*[1] brought physiology into the modern era, John, more than anyone since, wove the science of respiration together with the art of medicine. That union enabled his work to touch more lives than anyone our field has ever produced.



"When John [Severinghaus] became an anesthesiologist, the scientific foundations for our specialty scarcely existed. His life's work, more than anyone before him, laid and strengthened that foundation."

John, born May 6, 1922, in Madison, Wisconsin, was the first of the three children of Elmer and Grace Severinghaus. Elmer was an endocrinologist at the Wisconsin General Hospital, giving John memories of Ralph Waters, anesthesiology's first professor, at a time when our field had little academic or scientific foundation.

He attended Haverford College in Pennsylvania from 1939 to 1943, refocusing from a possible future as a physician like his father to physics and then doing radar-related research at MIT. The detonation of the atomic bomb on Hiroshima in 1945 was for John a tipping point, turning him away from physics back toward a life in medicine with a biophysics emphasis on the use of electronics in biology and medicine.

He began medical school at the University of Wisconsin and then transferred to Columbia University in New York, graduating in 1947. Residency followed at the University of Pennsylvania under the direction of Robert Dripps. As a resident, John devised a simple spirometric method to measure the uptake of the anesthetic gas nitrous oxide, presenting this research at a national meeting while his proud father sat in the audience.[2] This study may well have been the catalyst underlying the investigative career of John's most distinguished research trainee, Dr. Edmund (Ted) Eger, and ultimately Ted's and Larry Saidman's conception of minimum alveolar concentration.[3]

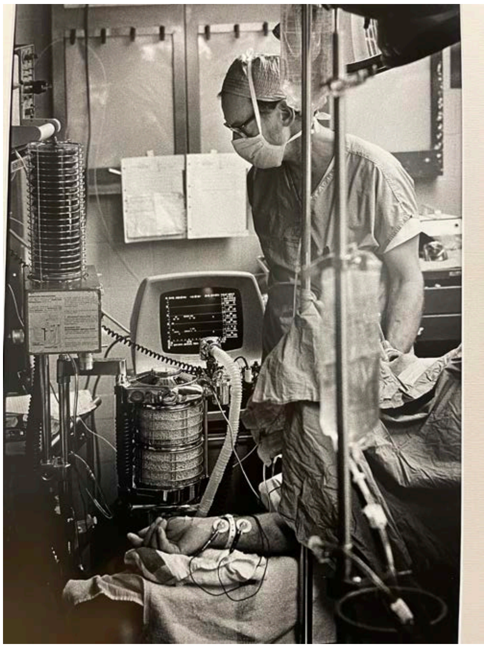
After 6 months of clinical training in anesthesia, John entered the laboratory of Dripps's colleague, Julius Comroe, one of the world's leading respiratory and cardiovascular physiologists. Comroe enabled John's assignment to the Public Health Service, based in the Clinical Center of the National Institutes of Health when it opened in July 1953. Only partly trained in clinical anesthesia, John was appointed Director of Anesthesia Research. There he met Stuart Cullen, who was then the chair of anesthesia at the University of Iowa. Three years later, John joined Dr. Cullen's department to complete his clinical anesthesia residency and begin his academic career.

When Comroe was recruited to the University of California San Francisco Medical School in 1958 to create the Cardiovascular Research Institute (CVRI), John was one of the bright, young scientists he induced to join him. This move came coupled with the recruitment of Stuart Cullen to affect the conversion of anesthesia at UCSF from a division of the Department of Surgery to a freestanding department. What followed for John was

Image: American Society of Anesthesiologists.

Accepted for publication July 13, 2021. From the Department of Anesthesia and Perioperative Care, University of California at San Francisco, San Francisco, California (P.E.B.); the Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington (T.H.); and the Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, California (L.J.S.).

a lifetime of adventure as a clinician, educator, and most-of-all searcher for understanding. He played a major role in the maturation of the CVRI and UCSF's Department of Anesthesia, both of which quickly became leaders on the national scene.



In 2008, as a measure of the esteem in which his research was held, the American Society of Anesthesiologists created a new lectureship at their annual meeting: the John W. Severinghaus Lecture on Translational Science. John was its first lecturer with a talk entitled Bench to Bedside: Gadgeteering for Healthcare.[4]

In reminiscing on his life as a translator of technology to medical science, John touched on a number of examples, among them an electrophrenic nerve stimulator to effect noninvasive artificial ventilation,[5] transcutaneous monitors of P_{O_2} and P_{CO_2}[6] a complex circuitry of thin tubes to deliver breathing gases from patients in multiple operating rooms to a centrally located mass spectrometer to monitor anesthetic gas concentrations including end-tidal carbon dioxide,[7] methods for assessing the accuracy of pulse oximeters,[8] and the Severinghaus blood-gas calculator, a slide rule permitting respiratory and metabolic acid-base quantification on one side and blood oxygenation on the other. These calculations are now part of every blood-gas report.[9] These extraordinary contributions remain in the fabric of our daily clinical lives.

In 1954, at a meeting of the American Physiologic Society in Madison, Wisconsin, John encountered Richard Stow. Stow developed an electrode to measure the partial pressure of carbon dioxide in blood or other fluids by placing a gas-permeable membrane over the end of a pH electrode; carbon dioxide diffused through the membrane to change the pH of the water bathing the pH glass. The problem, Stow found, was that the electrode was unstable and insensitive. John suggested adding a bicarbonate buffer to the water. Problem solved, and what became known as the Stow-Severinghaus P_{CO_2} electrode was born.[10]

Two years later at a gathering John assembled, Leland Clark reported on his work with a P_{O_2} electrode, an oxygen polarograph with a platinum tip covered by a gas-permeable membrane to prevent blood from "poisoning" the electrode tip. Until the tip was miniaturized to decrease its oxygen consumption, samples had to be stirred or flowed continuously past the electrode tip.[11]

As John's inventions go, one is in a league of its own: the blood-gas analyzer. Facilitated by John's development of a stable P_{CO_2} electrode, the device that John and his technician, Freeman Bradley, produced enabled measurement of the P_{O_2}, P_{CO_2}, and pH of blood easily and rapidly. This resulted in a major transition in the practice of medicine, namely bringing physiologic assessment and titration of care into the realm of assessing and managing the cardiovascular, pulmonary, and renal status of high-risk, critically ill patients.[12]

Blood-gas analysis allowed surgical and other interventions that would have led to serious morbidity and even death in an earlier time. Not only was anesthesiology transformed from art to science, but the entire field of critical care medicine followed. This evolution is akin in impact to the discovery of antibiotics, anesthetics, and asepsis, and produced a sea change in what medicine could do to save lives. A prototype of a blood-gas machine with the Severinghaus/Stow electrode, the Clark oxygen electrode, and a pH electrode resides in the permanent collection of the Smithsonian Institution.

Beyond invention but truly enabled by it, John had grown curious about how breathing and brain blood flow were regulated during acclimatization to the hypoxia of high altitude. Studies were performed on human volunteers (read: each other) after rapid ascent from sea level to the Barcroft laboratory at 12,470 feet in the White Mountains near Bishop, California, gifting John a near-disabling headache after spinal puncture to measure the pH of his cerebrospinal fluid. These studies in the 1960s were catalyzed in part from those of his colleague Bob Mitchell, who, together with Hans Loeschke, discovered the existence of carbon dioxide–sensing receptors on the ventrolateral surface of the brainstem of cats.[13] This carbon dioxide responsivity led to the question of what role pH played in increased breathing after a very few days of exposure to high altitude.[14] Later studies folded regulation of cerebral blood flow[15] into this same model. John became a leading authority on the acid-base balance in the body, collaborating in research and writing with leading Danish scientists Poul Astrup and Ole Sigaard-Anderson. With Astrup, John produced a book entitled *The History of Blood Gases, Acids and Bases*.[16]

Throughout this feast, John touched and enriched the lives of many others, both his own mentors, Comroe, Cullen and Dripps, and his contemporary colleagues, Bob Mitchell, F. J. W. Roughton, and Niels Lassen. Many younger scientists, among them Chuck Richardson, Cedric Bainton, George Gregory, Soren Sorenson, John Feiner, and Phil Bickler, were inspired and sustained by John.

As John aged and his curiosity (if possible) broadened, his interest in the historical antecedents of his scientific life ripened. He became an inspiring voice on precious moments of discovery, focusing in particular on the history of high-altitude research, including his own at the Barcroft Laboratory and in Peru, and on the history of the discovery of oxygen. His publications and presentations continued well into his 90s.

When John became an anesthesiologist, the scientific foundations for our specialty scarcely existed. His life's work, more than anyone before him, laid and strengthened that foundation. His many contributions are not only woven into the foundation of our daily work but form cornerstones for the modern basis of respiratory physiology and critical care.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Bickler: philip.bickler@ucsf.edu

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