ANESTHESIOLOGY

Savoring Uncertainty

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Although I couldn't have imagined it at the time, the seed for my research on the chemical control of breathing was planted in 1944 when my parents put 13-yr-old Tommy Hornbein on a train in St. Louis, Missouri, and sent him off to a camp in Colorado (fig. 1).

Looking back, discovering mountains has been the major pivotal event of my life. Those high hills became my spiritual home, underpinning all that followed: mountaineering, medicine, research, family, and community.

During my high school years, I voraciously read accounts of attempts to climb high mountains, wondering how humans could even survive at the summit of Mount Everest, much less climb there.

After graduating from high school in 1948, I attended the University of Colorado (Boulder, Colorado) to become a geologist, spending spare and some not-so-spare time exploring the rocks and peaks in Boulder's backyard. I soon became involved with the creation of one of the first mountain rescue units in the United States, learning and then teaching first aid. At the end of my junior year, I changed my major from geology to premed and applied to my hometown medical school, Washington University (St. Louis, Missouri). Although lacking much of the usual premedical course work, I was accepted to join the class that started in the fall of 1952. Looking back, the main thing I took away from my college years was to learn about myself, to dream, and to get high on uncertainty.

Fig. 1. Dr. Thomas Hornbein returned to Colorado after retiring from the Departments of Anesthesiology and Physiology and Biophysics at the University of Washington School of Medicine, where he served as Chairman of Anesthesiology from 1978 to 1993. Photograph by Dale Johnson, courtesy of Thomas Hornbein.

In medical school, I began to explore the scientific literature on how humans adapt to high altitude. Questions arose. Thoughts of becoming a doctor practicing in a small mountain town succumbed to a growing curiosity about altitude acclimatization. I read Paul Bert's account of the tragic flight of the hot air balloon Zenith in 1875, and the writings of Haldane, Barcroft, Henderson, and Heymans, who received a Nobel Prize in 1939 for discovering the role of the carotid bodies. I found more contemporary studies by a trio at the University of Pennsylvania (Philadelphia, Pennsylvania)—Julius Comroe, Carl Schmidt, and Robert Dripps, who was Chair of Anesthesiology there.

An observation by a Peruvian investigator, Hugo Chiodi, that high-altitude natives breathed less vigorously and had higher blood hemoglobin concentrations than lowlanders acclimatized to the same high altitude caused me to wonder: Might the highlanders' polycythemia cause their lesser ventilation? In my senior year, I opted to use my 6 wk of elective time to answer that question.

I sought the advice of Albert Roos, a respiratory physiologist with an insatiable curiosity and a bubbling joy at poking and prodding the unknown. Dr. Roos was born in Holland, obtained an M.D. degree there, became a consummate classical pianist, and was sent by his parents to the United States just before the Nazi occupation. His father,

Quantitation of Chemoreceptor Activity: Interrelation of Hypoxia and Hypercapnia. By TF Hornbein, ZJ Griffo, A Roos. J Neurophysiol 1961; 24:561–8.

Abstract

The first quantification of neural discharge from the carotid body of cats in response to hypoxia, hypercapnic acidosis, and their combination discovered a strong potentiating effect of hypoxia and hypercapnic acidosis combined as compared to either alone. This paper was the start of a research journey that eventually examined the regulation of blood and cerebrospinal pH by peripheral and central chemoreceptors in the setting of systemic acid–base alterations. This research focus was the result of the author's personal fascination with mountains and human adaptation to high altitude—an interest that led to his own ascent of Mount Everest in 1963. The inherent uncertainty and challenge involved with climbing high mountains has served as a metaphor and inspiration for his life, including his career in academic medicine.

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This article is featured in "This Month in Anesthesiology," page A1. The work presented in this article has been presented at the Federation of American Societies for Experimental Biology Annual Meeting in 1960.

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a respected academic veterinarian/physiologist, was sent to Auschwitz.

Albert was game to provide guidance for a small project quite different from his studies of pulmonary gas exchange. His laboratory possessed all the tools needed: a stationary bike, a spirometer, the plumbing needed to connect a puffing peddler, and the devices for measuring exhaled gas concentrations. Over several days, I was transfused with five units of blood to raise my hematocrit from 45 to 60%. The higher hematocrit indeed resulted in lower minute ventilation, especially at higher workloads and an inspired oxygen concentration of 14%, equivalent to about 10,000 feet altitude (fig. 2).

My first scientific publication was accepted by the *Journal of Applied Physiology* and published 2 yr later in 1958, with one subject and no statistical analysis.[1] This hors d'oeuvre was the entrée to the major focus of my research life: the exploration of the role of chemoreceptors in regulating breathing at high altitude.

After anesthesia residency, I returned to Albert Roos's laboratory as a National Institutes of Health (Bethesda, Maryland)–supported research trainee. The initial question I sought to answer was whether diminished breathing with polycythemia could be explained by decreased discharge from peripheral chemoreceptors.

But first I had to learn how to find, dissect out, record from, and quantify discharge in the nerve transmitting output from the carotid body to the medullary respiratory center. Next, I had figure out how to determine pH, P_{CO_2}, and P_{O_2} in arterial blood in an era that preceded the existence of blood analysis à la Severinghaus' electrodes. This, too, proved to be a nontrivial challenge.

We were able to produce the first quantitative descriptions of how the carotid body responds to hypoxia, hypercapnic acidosis, and the interaction between the two. The most significant discovery from this study was the potentiating effect of low Pa_{O_2} and high Pa_{CO_2} (*e.g.*, during breath holding or asphyxia) on carotid body discharge compared to hypoxia alone (fig. 3). Our paper, published in the *Journal of Neurophysiology* in 1961,[2] was designated a "Citation Classic" by *Current Contents* 25 yr later—a recognition based on its number of citations in subsequent scientific reports.[3]

After completing my research fellowship, I went to the U.S. Naval Hospital in San Diego (San Diego, California) as an anesthesiologist to fulfill a 2-yr service obligation that allowed graduating male doctors to complete specialty training first. I was discharged from the navy 8 months early to join an expedition that made the first American ascents of Mount Everest in 1963.[4] Returning from that expedition, our family headed north to Seattle, Washington, for my first and only job at the newly created Department of Anesthesiology at the University of Washington School of Medicine.

I was eager to embark on my life in academic medicine and to return to exploring chemoreceptors and ventilatory adaptation to hypoxia. For the next decade, I was supported by a National Institutes of Health Research Career Development Award. I still hoped to find out whether polycythemia diminished carotid body discharge.

Alas, that study never came to be—a consequence for which John Severinghaus must share the blame. In 1962, John and three colleagues ascended from sea level to 12,470 feet at the Barcroft Laboratory on White Mountain above Bishop, California, to observe how blood and spinal fluid pH changed during acclimatization. At the price of a five-star spinal puncture headache for the principal investigator (Dr. Severinghaus), they observed that lumbar spinal fluid pH was quickly restored to near its sea-level norm far more rapidly than blood pH, which relied on renal bicarbonate excretion to compensate for the respiratory alkalosis induced by hyperventilation.[5]

Was there some sort of active transport of hydrogen or bicarbonate ions across the blood-brain barrier that might explain how this rapid restoration of brain extracellular fluid

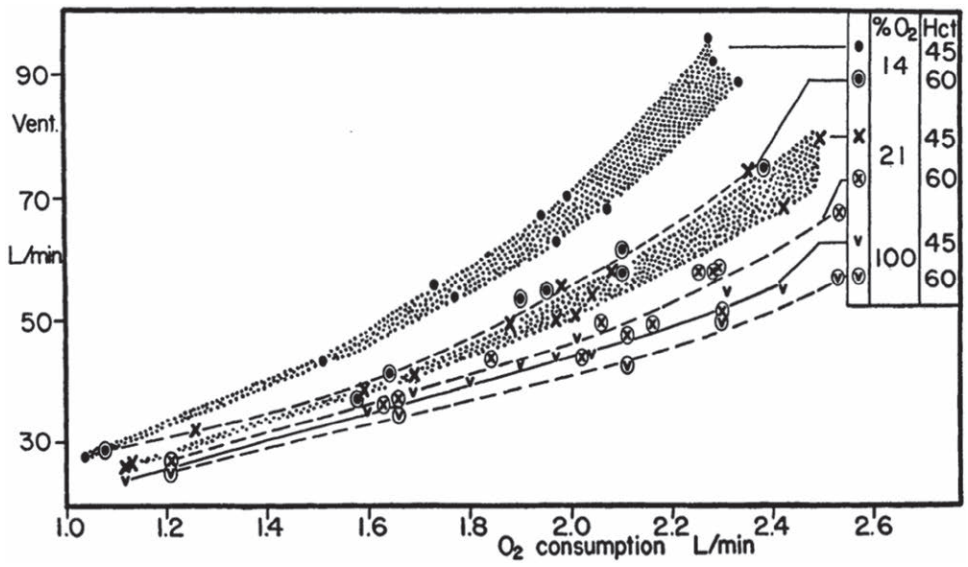

Fig. 2. Ventilation (Vent.; l/min) as a function of oxygen consumption (l/min) in the same individual, breathing 14%, 21%, and 100% oxygen at hematocrits (Hct.) of 45% and 60%. Reprinted from Hornbein and Roos[1] with permission.

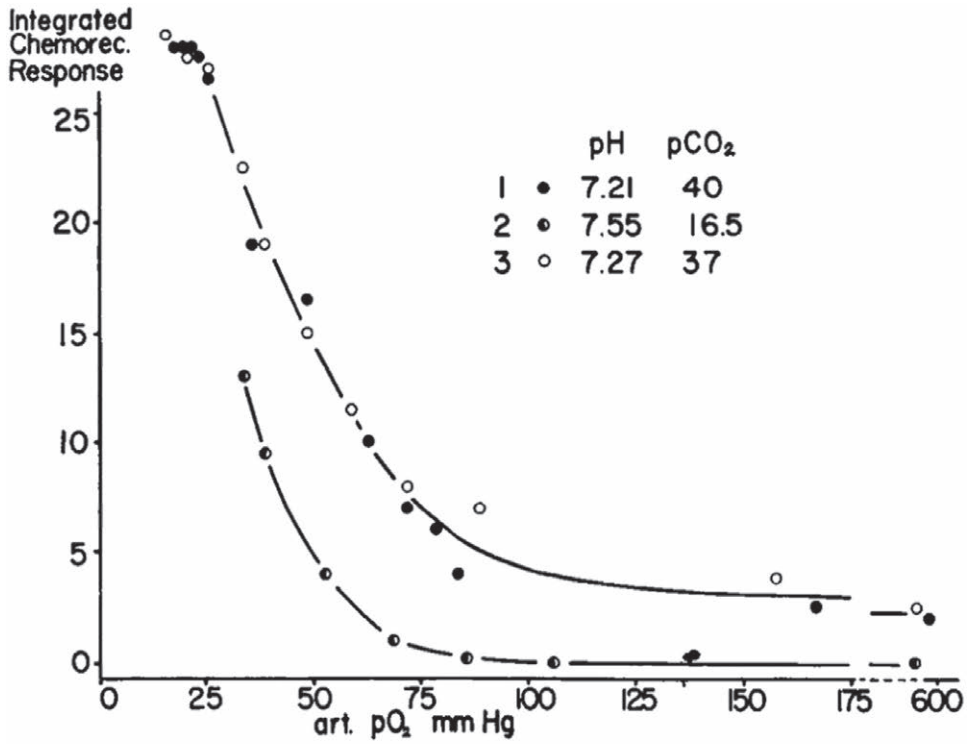

Fig. 3. Cat 2.7 kg. Integrated chemoreceptor response to changing P_{O_2} at different values of (H^+)-P_{CO_2}. Mean arterial (art.) blood pressure was 130±15 mmHg (SD). Reprinted from Hornbein *et al.*[2] with permission.

pH occurred? Or was it a simple passive process? Seeking an answer to this question moved my research target from the carotid body to exploring how rapidly the pH of brain extracellular fluid (cerebrospinal fluid) changes in response to systemic acid–base alterations. These studies began during a sabbatical in Copenhagen Denmark, with Soren Sorenson,[6] whom I had met when he spent a year as a fellow in John's laboratory, and were concluded by Ed Pavlin and me back in Seattle. Our findings were compatible with a passive regulation of extracellular pH across the blood-brain barrier.[7–10]

During those years, I found myself in a professional candy store replete with the enticing challenges of caring for patients, especially those at high risk, and in helping shape how we trained anesthesia residents. Those interests led, perhaps inevitably, to becoming involved with peers concerned with shaping the future of academic anesthesiology on the national scene. My personal research adventures ended in 1978 when I succeeded John Bonica as chair of our University of Washington department. Looking back, among the most precious rewards of my professional life were my collaborations and lifelong friendships with three mentors: Albert Roos (1914 to 2007), John Severinghaus (1922 to 2021), and John Bonica (1917 to 1994).

As for the title of this article, *Savoring Uncertainty*, discovering mountains was where it all began. In particular, my ascent of Everest in 1963 by a new, unknown path, and the story I subsequently told about a small group of like-minded individuals working toward a common goal,[4] has provided a marvelous metaphor for the ever-evolving pursuit of dreams.

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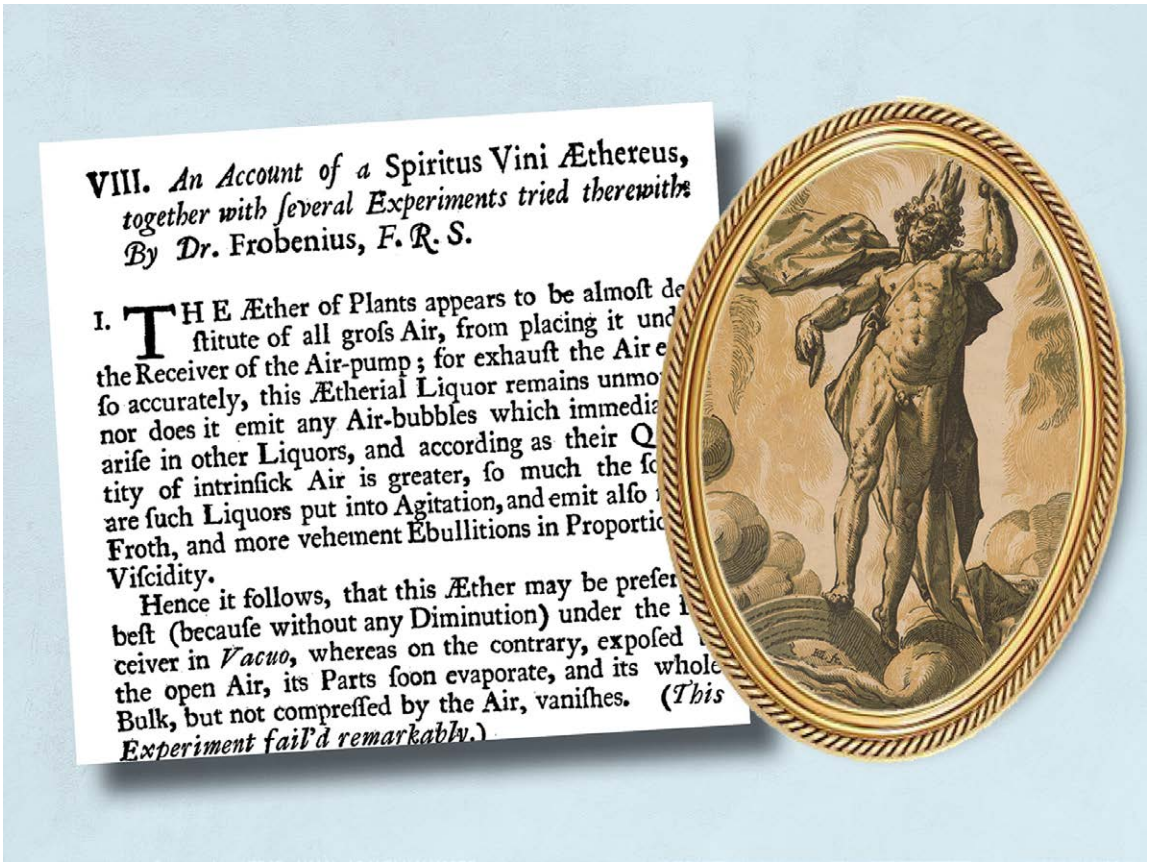
In the Spirit of Frobenius: *Aether* by Goltzius



By one account, Zeus's great-grandfather was the primordial Chaos, whose daughter Night (Nyx) and son Darkness (Erebos) begat two children. Named Day (Hemera) and Brightness (Aether), those offspring were respective opposites of their parents. Aether personified the brilliant blue atmosphere on and above the tops of mountains like Olympus. Around 1589 CE, Aether would be captured (*right*) in a woodcut created by a German-born Dutch artist named Hendrik Goltzius (1558 to 1617). Less than 2 centuries later in 1729, German chemist Sigismund Frobenius, M.D., F.R.S., inspired by the same deity, named an exceptionally flammable and volatile vapor, "Spiritus Vini Aethereus" (*left*). To Frobenius, *aether* seemed an other-worldly gas, "so volatile as it soon evaporates…it is the purest fire…it burns inextinguishably." Though intrigued by its chemical properties, physicians allowed ether's brilliant medicinal potential to linger in darkness until William T. G. Morton publicly demonstrated its anesthetic properties in 1846. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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