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JULIUS H. COMROE, JR.
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A Biographical Memoir by

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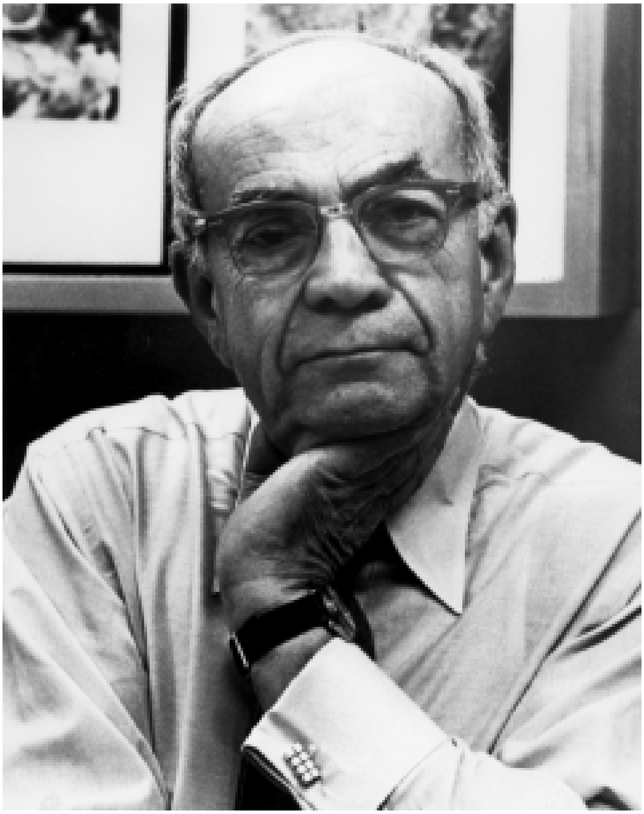
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JULIUS H. COMROE, JR.

March 13, 1911–July 31, 1984

BY SEYMOUR S. KETY AND ROBERT E. FORSTER

JULIUS COMROE WAS AN extraordinary teacher who began his medical career as a surgeon, then became an accomplished investigator and did important original research, but gradually directed his considerable energies into teaching basic biomedical research to graduate physicians and explaining its importance to medical practice and the acquisition of new knowledge. After developing the internationally recognized Cardiovascular Research Institute (CVRI) in San Francisco, he worked tirelessly, in spite of failing health during the last years of his life, to demonstrate to the Congress and the public, that investigator-initiated medical research was essential to improve the nation's health.

Julius H. Comroe, Jr., was born in York, Pennsylvania, on March 13, 1911, the youngest son of the city's preeminent internist. His father as well as his older brother, Bernard, had graduated from the University of Pennsylvania, both the college and the medical school, and were very loyal supporters of the institution. Julius naturally followed them and graduated first in his class from the college in 1931. As an undergraduate he was editor of the college humor magazine and demonstrated his penchant for cartoons by publishing a drawing of top-hatted stage-door

Johnnies outside the dressing room door of Penn's then all-male burlesque frolic, the *Mask and Wig Show*. At Penn Medical School he again graduated first in his class in 1934, and was admitted to the two-year internship program at the Hospital of the University of Pennsylvania. His goal was to become a surgeon, but during an operation on a patient with pelvic inflammatory disease one of Julius's eyes became contaminated. Rather than stay home and have it treated, he went to a surgical meeting in Chicago; the eye became desperately infected and had to be removed. This was the end of his career in surgery, to the benefit of medical science.

In 1936 Julius Comroe married Jeanette Wolfson, a tennis-playing friend and social worker; they had one daughter, Joan. His brother, Bernard, had been the first chief resident of the Hospital of the University of Pennsylvania, later becoming a widely known rheumatologist and author of a classic text. He was warmly regarded at Penn, an inspiration to Julius. Bernard's wife died tragically; he could not face life without her and followed her shortly, leaving his daughter an orphan. Julius and Jeannette moved into Bernard's house to take care of their niece, so that she would not suffer the loss of her home in addition to the loss of both parents.

As a medical student, Comroe had collaborated on a paper on the effects of mecholyl (1933) with Isaac Starr, the professor of clinical therapeutics and a member of the faculty of pharmacology. In 1936 he sought and was given an appointment in the Department of Pharmacology as instructor by Alfred Newton Richards. He began his research there investigating the control of respiration with Carl Schmidt, who was already established in the field. Corneille Heymans in Belgium had reported that lowering the oxygen content of blood flowing to the region of the bifurcation of the common carotid stimulated ventilation in animals, for which finding he won the Nobel Prize in 1938. The precise region in which the change in oxygen was detected and the relative importance of blood O_2 partial pressure (P_{02}) versus O_2 concentration was a matter of dispute. With the help of W. H. F. Addison in anatomy (1937), Comroe and Schmidt (1938) showed that it was the tiny carotid body that was sensitive to a fall in blood Po_2 and to a rise in blood Pco_2. This was an emergency system to protect against a fall in arterial Po_2 as contrasted with O_2 concentration and had little effect on normal respiration. These concepts of the function of the carotid bodies have held up over the years, established Comroe's reputation in the field, and helped him win a travel fellowship to the XVI International Physiological Congress in Zurich in 1938 and a Commonwealth Fellowship to work with Sir Henry Dale in London in 1939.

In 1927, before they reported chemosensitivity in the carotid bifurcation, Heymans and Heymans had also described a chemosensitive mechanism in the aortic arch region, but these results were challenged; so the existence of aortic chemoreceptors was in dispute when Comroe started his investigations. Again in collaboration with Addison (1938,1), Comroe carried out detailed anatomic studies of the aortic chemoreceptor, particularly to determine its blood supply, which was shown to be from the aorta in dogs and from the coronaries in cats. Thus armed, Comroe was able to identify their function by injecting at different sites in the great vessels and by blocking blood flow to the aortic chemoreceptive area (1939). This was the definitive work on the aortic chemoreceptors, showing they caused an increase in ventilation when arterial P_{O2} fell, or known chemical stimulators of the carotid body such as lobeline or NaCN were added to the blood. This stimulation of ventilation was less than that when the carotid body was similarly excited.

Schmidt and Comroe wrote several reviews summarizing their important work on the regulation of ventilation (1939,2; 1940; 1941).

Comroe also investigated the sensitivity of the central respiratory center located somewhere near the dorsal surface of the medulla (the fourth ventricle) (1943,1) to micro injections of solutions containing P_{CO2}, which produced a marked increase in ventilation of cephalad to the obex, restricting the central chemoreceptor to this region. Acids were less effective and lobeline ineffective. This led to the general conclusion that the arterial Pco_2 of blood perfusing the medullary region of the brain stem is the major determinant of normal ventilation, and that the function of the peripheral chemoreceptors was to protect the brain against hypoxia.

Comroe and Schmidt now had evidence for the control of respiration at rest by arterial P_{CO2} and P_{O2} and next tackled the ongoing problem of how ventilation is regulated during exercise, when these blood gases are essentially normal in the face of a massive hyperventilation. They sought the explanation in increased nerve traffic from contracting muscles and did find that stimulating peripheral muscle groups in man and anesthetized animals did increase ventilation, but not enough to account for the total increase seen in exercise (Comroe and Schmidt, 1943,2).

Comroe added on to his natural abilities as a teacher the experience gained in the outstanding pharmacology course of Richards and Schmidt. When he first joined the department he was given charge of the moribund course in materia medicae and made it into a popular offering. As in all his teaching he showed that ingenuity and careful preparation were essential.

In 1944 Comroe and Robert D. Dripps applied the most modern techniques of the time to the measurement in humans of arterial and alveolar P_{O2}, whose difference had been the subject of an intense disagreement between August Krogh in Denmark and J. S. Haldane in Oxford from the 1890s until the 1920s (1944). Krogh believed O_2 diffused passively from alveolar gas to capillary blood. In this case arterial P_{O2} should be less than or possibly equal to alveolar gas P_{O2}. On the other hand, Haldane believed that O_2 could be secreted from alveolar gas into capillary blood against a P_{O2} gradient. In this latter case, arterial P_{O2} should be greater than alveolar. Collection of arterial blood from humans without surgery was first reported in 1912; the measurement of P_{O2} in blood had only recently become possible. Comroe and Dripps equilibrated a small bubble of gas with 500 times its volume of arterial blood and then measured the O_2 in the bubble, finding that at rest at sea level, the arterial P_{O2} was 97.1 mm Hg and alveolar 97.0 mm Hg, not significantly different. This work was the start of a lifelong collaboration.

Dripps eventually moved to anesthesiology within the Department of Surgery, facetiously saying he could not see eating lunch out of a brown bag all his life. His colleagues in pharmacology gave him a going-away party at which Comroe gave him a large wooden mallet with a tag saying "If all else fails, try this." The two men published many further papers together on clinically applied physiology and pharmacology, particularly related to anesthesiology, until Comroe left Philadelphia in 1957, but their joint productivity continued for the rest of their lives in spite of the 3,000 miles separating them.

From 1944 to 1946 Comroe consulted for the Chemical Warfare Service, with a number of other distinguished pharmacologists and physiologists. This work related to the nerve gases, and he wrote a series of papers on the effects of fluorophosphate compounds on the eye (1946,1; 1946,2), for example.

By 1946 he had been a faculty member of the Department of Pharmacology for 10 years and was still an assistant professor in spite of a growing reputation as an investigator, teacher, and writer. When the possibility of becoming professor and chairman of the Department of Physiology and Pharmacology of the Graduate School of Medicine of the University of Pennsylvania appeared, he took it in spite of advice from Richards. The Graduate School of Medicine (GSM) at Penn was an unusual organization that had been founded in 1912 by the university at the urging of Provost Edward Fahs Smith, partly in response to criticism in the Flexner report about graduate medical education and with the hope of obtaining foundation support. Additionally, two non-university-affiliated medical schools in Philadelphia had their buildings condemned for urban reconstruction and were willing to turn their assets over to the University of Pennsylvania with the stated goal of providing organized didactic training for graduate physicians, particularly in basic science. The university took over these assets and ultimately built a new Graduate Hospital as part of the GSM. The school had extensive clinical and basic science faculty with affiliations to other medical schools in Philadelphia and faculty in each of the basic sciences. The physical facilities for these basic science departments, which were in the buildings of the School of Medicine, were meager. Comroe hoped to expand the student body and the facilities. He was aware of the need for physicians returning from World War II for re-education. He also knew of the accumulated research and instrumentation in government laboratories and the potential benefits to medicine this represented, plus the opportunity it offered for his department to apply it clinically.

Comroe started by assembling a detailed manual describing new instrumentation and classical methods of measuring pulmonary function in health and disease written by individuals who had been developing them during the war. He included comments on each short article from other investigators, so that the little volume entitled *Methods in Medical Research* (1950) presented the opinions of some two dozen individuals in the field. This small volume established his department as a leading center of pulmonary physiology and its application in lung disease.

As chairman of the Department of Physiology and Pharmacology of the Graduate School of Medicine, Comroe directed his efforts in two directions. First, he built a strong research faculty. Seymour Kety joined him from the Department of Pharmacology in the School of Medicine and helped him obtain instruments for the rapid and continuous analysis of respiratory gases at the mouth, including a nitrogen meter developed by John Lilly of the Johnson Foundation at Penn; a breath analysis mass spectrometer, the first practical one of its kind (now in the DeWitt Stetten, Jr., Museum of Medical Research of the National Institutes of Health), which could rapidly analyze any respired gas; and an infrared CO analyzer. He then recruited faculty to use these instruments, first Ward S. Fowler, who dissected the distribution of inspired gas in the lungs with the nitrogen meter (1951). Next, he recruited R. E. Forster, who measured pulmonary diffusing capacity with the mass spectrometer and CO meter and later the rates of reaction of CO and O_2 with red blood cells.

Comroe also wanted to apply Boyle's Law to the measurement of lung volumes, air flow rate, and airway resistance. With Stella Botelho and Robert Nims, Comroe used a surplus bomber nose cone as a body plethysmograph. They then went on to have a more sophisticated body plethysmograph designed and constructed (now at the Smithsonian Institution) (1959), which A. B. DuBois instrumented and used to measure airway resistance, lung volume, and instantaneous pulmonary blood flow (1956,1,2,3). As the results of these investigations were reported, physicians from all over the world were attracted to Comroe's department. He also organized a number of short courses offering hands-on experience in pulmonary function studies. With the experience gained in teaching these courses, as well as the slides, illustrations, and diagrams used, Comroe and his junior colleagues produced a thin book on pulmonary physiology and pulmonary function testing, *The Lung* (1955). An international success, the book was translated into several languages and eventually went through three editions. For the next 30 years Comroe collaborated on a long series of papers dealing with clinical applications of pulmonary physiology.

The second direction of his efforts was to develop new methods of teaching basic medical science to graduate physicians. With colleagues in the several disciplines (Seymour Kety, David Drabkin, William Ehrich, Oscar Batson, and John Flick), he was the prime mover in developing an organized didactic course in the GSM, which presented up-to-date basic science for graduate physicians, most of whom had just returned from years in military service. This new course was structured around the major organ systems rather than around departmental disciplines, with lectures and discussion proceeding logically through the basic sciences pertinent to each organ system: anatomy, histology, physiology, pharmacology, microbiology, and pathology, with frequent clinical correlations. Hence, it was called the Correlated Basic Sciences Course. The course, and concomitantly the graduate school, were very successful, having a class of 300 students at the school's peak.

Comroe organized and presented this correlated basic sciences course at the first teaching institute of the American Association of Medical Colleges (1954). Western Reserve Medical School in Cleveland took up the new system concept in the reorganization of its curriculum for medical students. In recent years, several other leading medical schools have developed similar courses with a flourish. It must be emphasized, however, that this course was designed for graduate physicians who had already received a solid foundation in basic medical sciences and not for college graduates just entering medical school.

Cuthbert Bazett, chairman of physiology at Penn, died en route to an IUPS Congress in England in 1950, and Comroe was obviously a strong candidate to succeed him, however he was told confidentially that some of the senior faculty were opposed to his selection and that he would not be offered it. He had ambitious plans for the GSM, particularly in terms of interesting clinicians in doing research and training them to do it. He developed a plan to merge the Philadelphia General Hospital next door with the GSM and expand graduate medical training. This ran into intense opposition from the School of Medicine. By 1956-57 it was clear that the university was opposed to any expansion of the GSM and even to its continued existence. The flux of World War II veterans had fallen off to be replaced by graduate physicians from abroad seeking advanced training, a service in which the university was even less interested.

At this point Julius Comroe was seeking new opportunities. He was invited to look at the chair in pharmacology at the Medical School of the University of California in San Francisco. At that time the UCSF was a divided school with the clinical departments in San Francisco and the basic science departments in Berkeley across San Francisco Bay, where they had moved after the 1906 earthquake. The university was building a new basic science campus and teaching hospital in San Francisco, and Comroe was shown the shell of the hospital and the vacant thirteenth floor, which could not be used for patients. He was discouraged by the philosophy of the entrenched pharmacology faculty and decided not to accept the position. On the way back to the airport Dr. Ellen Brown of the Department of Medicine, who had shown him around, asked him for the names of possible candidates for director of a new cardiovascular institute that the University of California planned to establish in the empty thirteenth floor of the new hospital. Comroe said “me.” Comroe was a pulmonary physiologist, not a cardiovascular physiologist, but as he said frequently, blood flows through all the organs.

He was offered the directorship and proceeded to develop a world-class research institute in San Francisco, which had an enormous influence on the flowering of the whole medical school. During the 26 years he was in San Francisco, what had been a minor provincial institution became one of the best in the United States, with a national and international reputation in medical research and teaching. As Comroe himself pointed out (1983), it took many individuals to produce this change, and there were also propitious societal changes at the time, such as the burgeoning NIH support for research. A determining factor, however, was his constant demand for the highest scientific standards in recruitment and promotion, for which he fought on all fronts and for which many of his colleagues give him full credit. At the time he arrived in San Francisco the school had been accustomed to take a long time to make a new appointment and then it was generally internal. Comroe sought to have national searches for active, productive investigators wherever they might be. This meant that he ruffled many feathers, further handicapping his administrative advancement.

A generic problem of research institutes in a medical school is the potential competition it represents to the research programs of individual departments. Comroe was sensitive to this and used the CVRI to help departments build strong research programs, providing space and funds, but always insisting on the highest scientific standards. Not every department thanked him for his efforts.

The snail-paced bureaucracy of the University of California System was legendary in academic circles, and Comroe soon ran into it after his arrival. His response was typical. He collected data from other universities to demonstrate how long it took a research proposal to pass through the different levels of their administrations, compared these figures with the much longer delay at the University of California, and presented the results to President Clark Kerr; that particular problem was soon remedied. Kerr on several other occasions was very supportive of the CVRI.

After he moved to San Francisco and took on increased administrative responsibilities, Comroe did less research with his own hands, and in the late 1960s gave up his own laboratory. He did not abandon research, but held weekly meetings with the research trainees and the faculty to keep each one abreast of what the others were doing. What he lacked in the minute details of methodology he made up for with his broad views of how research is accomplished. However, he collaborated in a number of original articles, particularly in his first area of interest, the control of respiration and the chemoreceptor (1971).

His activism—speaking and writing in support of basic medical research—expanded enormously. He wrote a series of articles entitled "Physiology for Physicians" in the *New England Journal of Medicine* from 1963 to 1969. Comroe became increasingly concerned about the micromanagement of research by government and business, which were directing the research toward specific societal needs of the moment to the detriment of future unpredictable discoveries, their model being NASA's successful engineering program to put a man on the Moon. While on the National Heart Council, he realized how important it was to convince Congress and the public that supporting scientific study at the basic level was actually very practical. In 1971 his old friend Robert Dripps spent a sabbatical at the CVRI; he and Julius Comroe, using scientific and scholarly methods, began a monumental effort to investigate how many of the important new contributions of clinical medicine since the 1940s had depended on research that had been stimulated with the aim of contributing to medical care and how many had been serendipitous. The resulting publication appeared in 1976 and included a careful analysis of 529 key articles that provided the supporting knowledge for advances in topics chosen by 40 physicians, reviewed in turn by 140 consultants, all in an effort to remove as much bias as possible. Comroe and Dripps found that for cardiovascular and pulmonary advances 41 percent of the crucial research was done without any goal to improve the practice of medicine. This argument for the support of basic non-clinical research still stands today. Comroe presented some of this material as editorials in a witty, pungent vein as views from his "Retrospectroscope" from 1974 until about 1978 in the *American Review of Respiratory Disease.* A collection of these was eventually published in a little volume titled *Retrospectroscope: Insights into Medical Discovery* (1977).

He himself supplied an example of an unexpected bonus to clinical medicine of ungoaled basic research. In 1958 with Elizabeth Carlsen he reported measuring the rate of uptake of NO by human red cells to determine the effect of cell size on ligand gas uptake. In 1980 Furchgott made the startling discovery of an endothelium-derived factor that dilates vascular smooth muscle, which turned out to be NO and is accepted as a central mechanism in the regulation of local blood flow. An important facet of its physiologic function is that it be removed rapidly by practically irreversible combination with hemoglobin in red cells, localizing its action to the site of its secretion. The data of Carlsen and Comroe prove this.

Comroe continued teaching to fellows in the CVRI and on the national scene, He delighted in cartoon slides to illustrate a point. Possibly the most famous is a drawing of a growling and ferocious visage with the legend "Your suggestions are gratefully received." This probably represented his impression of medical school administrators. He took efforts to present complicated matters simply; his oft repeated dictum was that it is better to make it clear to students that to make it precisely correct. In Philadelphia, and later in San Francisco, he presented courses for physicians in such practical topics as how to lecture and how to write scientific articles, using tape-recorded and later video-recorded lectures for self and group criticism. He had a bag of histrionic tricks to make a point such as dropping a large pile of advertisements from pharmaceutical companies on the floor at the start of his lecture to emphasize their efforts to influence therapeutic decisions. One time he realized that the participants in a journal club were not reading the assigned material ahead of time. At the next meeting he announced there would be an exam that day. The one question was to write down the color of the book containing the article. Most flunked but none forgot.

Julius Comroe published nearly 200 scientific articles in his lifetime and wrote 4 books. He was asked to give many distinguished named lectures, was elected to the National Academy of Sciences, the American Academy of Arts and Sciences, and as a fellow of the Royal Academy of Physicians.

He was instrumental in forming the Institute of Medicine and served on its first Executive Committee. He received honorary degrees from the Karolinska Institute, the University of Chicago, and the University of Pennsylvania. He was also awarded the distinguished Jesse Stevenson Kovalenko Medal for medical science of the National Academy of Sciences.

In the 1960s Julius Comroe developed severe back pain that would not yield to conservative therapy and he would not consider surgery. By the 1970s this pain had become so severe that he could not carry on as director of the CVRI, and in 1973 he retired. In 1976 a symposium was held in his honor, bringing together his fellows and colleagues from around the world. Shortly thereafter he was found to have cancer of the prostate, it was treated surgically but by 1983 it had spread to his spine and he was confined to bed for the remainder of his life. He continued writing, however, and produced a humorous description of the birth pangs of the CVRI and a modest description of his part in the ascent to excellence of the School of Medicine of the University of California, San Francisco. He died in 1984; although he discouraged friends from trying to establish a chair in his name (saying they should choose a rich man as they could then raise more money), there is now a Comroe chair at the School of Medicine of the University of California in San Francisco and a student scholarship at the School of Medicine of the University of Pennsylvania given by the Class of 1948. At and after the twenty-fifth anniversary of the CVRI, Jeannette Comroe received hundreds of letters from all over the world attesting to the love and warmth that his colleagues and students held for him, a fitting tribute to a life spent in science and teaching.

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