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Giants in Chest Medicine: Karlman Wasserman, MD, PhD, FCCP

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Karlman Wasserman was born in Brooklyn, New York in 1927. He graduated from high school in June 1944 and, at the age of 17, at the height of World War II, he joined the U.S. Army Specialized Training Reserve program. Before he was able to complete his studies in engineering at Princeton University he was called to active duty, serving in the postwar Army of Occupation in Japan from September 1945 to December 1946.

Karlman used the “Servicemen’s Readjustment Act”, also known as G.I. Bill, to complete his undergraduate education at Upsala College, NJ, in 1947, majoring in chemistry with a minor in biology. A subsequent move to Tulane University provided a post-graduate training in physiology in 1948, and kindled life-long interest in experimental physiologic research.

At Tulane, under the supervision of Dr. Mayerson, Karlman’s research focused on capillary permeability and the transfer of macromolecules such as albumin between the vascular and lymph compartments after acute changes in blood volume. He used newly available radioactive tracer molecules to provide precise measurements of plasma volume and of albumin leakage from the blood. On the strength of these studies, Karlman was awarded a PhD in Physiology in 1951, and embarked on an academic career studying respiratory physiology.

By this time, the Korean War had already begun, and Karlman was approached by the U.S. Army to help improve the treatment of acute hypovolemic shock in field hospitals. Dextran was being used in replacement fluids after blood loss, due to its low incidence of allergic reaction. Karlman’s studies demonstrated that plasma expansion could be improved when experimental animals with acute hypovolemic shock were infused with large molecular weight fractions of dextran, these being un-extractable by the kidney – a valuable finding to help progress the care of wounded soldiers, as well as civilian patients with traumatic injury.

From 1951 to 1953 Dr. Wasserman broadened his research experience to include comparative renal and cardiovascular physiology, by undertaking a series of summer placements at the Marine Biological Laboratory in Salisbury Cove, Maine. He worked on active renal tubular transport mechanisms in the flounder and on the diving reflex in the seal. It was at Tulane in 1952 where Karlman met his beloved wife Gail. He later secured a place at Tulane Medical School in 1954, and had the singular honor of being both a member faculty in the Department of Physiology and a student at the Medical School at the same time.

Following graduation in 1958, Dr. Wasserman began his Internship in Internal Medicine at Johns Hopkins University in Baltimore. Soon after, the now-world-renowned Cardiovascular Research Institute (CVRI) was formed at the University of California School of Medicine in San Francisco, and the new Director, Dr. Julius Comroe Jr., offered Karlman a special fellowship to continue his medical training on the west coast. At CVRI, Wasserman and Comroe developed a new method for non-invasive measurement of pulmonary capillary blood flow. They demonstrated the pulsatility of pulmonary capillary blood flow and its diminishment by increased pulmonary vascular resistance: Observations that resolved an ongoing debate of whether capillary blood flow in the low-pressure pulmonary system was pulsatile or continuous during a cardiac cycle.

In the early 1960s the incidence of heart disease was rapidly increasing in the United States, and there was a desperate need for methods to detect early signs of the failing heart. Following a nudge from his mentor, Karlman set about to address this issue: A decision that would set his trajectory to become a leading light in field of exercise physiology and medicine. Dr. Wasserman hypothesized that heart failure could be detected by an early onset of anaerobic metabolism during exercise, reflecting a paucity of oxygen supply relative to demand in the peripheral muscles consequent to the circulatory impairment imposed by the failing heart. The key was to expose the mismatch using an external stressor (exercise) and reveal it using pulmonary gas exchange measurements. The coupling of internal to external respiration would allow Dr. Wasserman to demonstrate a "threshold of anaerobic metabolism" during exercise - a thought that, in the course of time, led to the now established clinical concept of the "anaerobic threshold". Dr. Wasserman's original description of the anaerobic threshold concept was in cardiac patients and published in the American Journal of Cardiology in fall of 1964.

Achieving the breath-by-breath gas exchange measurements that would become the world standard in exercise testing, however, was technically demanding and would take almost 10 more years of work to realize. Rapidly responding oxygen analyzers, needed to measure the rapidly-fluctuating gas tensions at the mouth, were not yet readily available. What is more, in the early 1960s, "a computer" was still a job description, not an automated means of digital data processing! Dr. Wasserman joined the faculty of Stanford University as a Respiratory Physiologist, and secured an NIH grant to set-up a respiratory function laboratory. A physicist working with digital computers at Central Research at Varian Associates in Palo Alto, Dr. William Beaver, soon became a key collaborator. Working together, the concept of real-time breath-by-breath gas exchange measurements during exercise began to take shape. Publications began to flow from this newly minted collaboration, advancing the use of exercise gas exchange measurements as a clinical investigative tool. The comprehensive overview that encapsulated integrative physiology as perhaps fewer others have managed since was the Interaction of Physiological Mechanisms during Exercise published in 1967. Tucked into the penultimate page of the article was the now eponymous graphical concept: Wasserman's gears presented three interdigitated systems, representing the integrated functioning of ventilation, circulation and muscle metabolism during exercise. The figure, ubiquitously cited and reproduced in numerous variations, has become the coat of arms of clinical cardiopulmonary exercise testing.

1967 brought a move to Harbor-UCLA General Hospital, where Dr. Wasserman was recruited to be the inaugural Chief of the Pulmonary Division. Karlman brought with him from Stanford a promising young pre-doctoral fellow to help drive his research program in Los Angeles. Together, over the next 25 years, Drs. Wasserman and Whipp produced a string of seminal papers underpinning the modern cardiopulmonary exercise test, and contributing immeasurably to the physiological basis of exercise limitation in health and disease. With the continued collaboration of Dr. Beaver at Varian, the method of online computer analysis of breath-by-breath exercise gas exchange was finally realized in 1973. Later came the method for non-invasive detection of the anaerobic threshold by gas exchange, which, at the time of writing, is the most cited article in the 68-year history of the Journal of Applied Physiology.

In the 1970s in Los Angeles, a surgical team had begun treating patients with severe bronchial asthma using bilateral carotid body resection, presumably for symptomatic relief – a method that would soon become obsolete. Nevertheless, these patients were to provide a unique model for the study of the mechanisms controlling ventilation during exercise. It was thought that the carotid bodies normally contributed some proportion of the total drive to resting and exercising ventilation in man. Dr. Wasserman's studies published in the New England Journal of Medicine falsified this hypothesis: human subjects without carotid bodies were able to effect a completely normal exercise hyperpnea. The control of the exercise hyperpnea, described by some in physiology as "the ultrasecret", remains a focus of Dr. Wasserman's program to this day. Later that decade, in 1977, the U.S. Department of Labor approached Dr. Wasserman's Division to evaluate a large cohort of Los Angeles shipyard workers who had been potentially exposed to asbestos. The evaluation was to include a quantification of exercise intolerance and, if significant limitation was present, a statement on the primary mechanism of limitation. The legacy of this project was to be a visual interpretation of exercise data by a standardized arrangement of graphs in a 3-by-3 array of panels that facilitated rapid and reliable clinical interpretation of an individual's exercise response. This graphical arrangement received worldwide recognition and later became known as the "9 Panel Plot". It was presented to the world in the seminal textbook Principles of Exercise Testing and Interpretation by Drs Wasserman, Hansen, Sue and Whipp, which is currently in its 5th edition. That a large number of these shipyard workers turned out to be in good health, provided an early set reference ranges, which have been used internationally to discriminate abnormalities on exercise testing.

With the success of his breath-by-breath gas exchange measurements and interpretive methods, Dr. Wasserman's lab at Harbor-UCLA began to receive a steady influx of visiting physicians, keen to learn from the master about clinical interpretation of exercise responses. This lead to the establishment in 1984 of Harbor Practicum; a multi-day practical and didactic course on exercise testing and interpretation. This course, together with versions adapted with colleagues for presentation in Japan and Europe, graduated its 101st class (67th from Harbor-UCLA) in October 2016, and continues to provide a forum for education and the sharing of ideas within the global exercise testing community.

Throughout his career Dr. Wasserman placed great emphasis on promoting collaboration in research and education, bringing together disciplines and bridging international borders. His work has been exemplified by interdisciplinary and international researchers working together to move the field forward. Collaboration was evident from his early work with Dr. Beaver in bringing the power of digital computing to bear on physiological questions of the day, through to the present day with physiologists, cardiologists, and pulmonologists coming together from afar afield as Germany, China, Japan, and the USA to advance the pathophysiologic understanding of rare diseases with both heart and lung involvement. In all, Dr. Wasserman has contributed to training more than 100 clinical researchers from all over the world. Members of this extended academic family continue to produce an enormous volume of interdisciplinary, high-quality research garnering worldwide recognition. Dr. Wasserman himself remains active in production of original research articles - over 65 years after his first paper was accepted for publication.

Dr. Wasserman became Professor Emeritus on Recall at David Geffen School of Medicine at UCLA in 1997. Despite his "retirement", his active involvement in medical research has not diminished. Karlman and Gail's four children also pursued careers in medicine, Sydlee and Wendy as Nurses, David is world-recognized expert in diabetes and Professor of Physiology at Vanderbilt University, and Ron is an Attending Physician in Infectious Disease in Northern California. Currently, one of their nine grandchildren is in medical training as a chest physician at Cedars-Sinai Medical Center in Los Angeles.

Throughout his career Dr. Wasserman underscored physiology as the central element to understand pathological processes, and consistently integrated this concept into his research and clinical practice. It should be no surprise that the Division that he helped to found carries the name of Respiratory and Critical Care Physiology and Medicine long after he stood down as Chairman. Dr. Wasserman's extraordinary achievements in respiratory and exercise physiology and medicine are well recognized. Perhaps less well lauded is his tenacity and drive in championing the discipline of physiology in the advancement and distribution of medical knowledge. Physiologists, cardiologists and respiratory physicians the world over are able to see further for standing on the shoulders of Dr. Wasserman's research. His unique ability of integrating ideas, concepts and people across disciplines and countries, make him a true Giant in Chest Medicine. We encourage all to view the interview to hear Dr. Wasserman's words of wisdom (Video X).

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