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Karlman Wasserman, MD, PHD, Physiologist and Physician-Scientist: 1927–2020

Dr Karlman Wasserman passed away at the age of 93 on June 22, 2020. He was one of a cadre of leading 20th century physiologists who not only advanced knowledge of respiratory and cardiovascular function but also tied that knowledge directly to the clinical arena. He was born in New York in 1927, did his undergraduate studies in chemistry and biology at Princeton and Upsala Universities, and earned his PhD in physiology working with Dr Hymen Mayerson at Tulane University. At Tulane, he learned classic experimental physiology through studies of blood volume, vascular permeability, and cardiovascular and renal physiology. After completing his doctorate, he joined the faculty at Tulane and also enrolled in the medical school, earning his medical degree in 1958. He completed his medical internship at Johns Hopkins University and was recruited directly from there to a research fellowship at the newly formed Cardiovascular Research Institute (CVRI) of the University of California at San Francisco. His mentor at CVRI was Dr Julius Comroe, another of the era's great integrative physiologists. Dr Comroe charged Dr Wasserman with identifying an approach to evaluating the growing clinical problem of heart failure, starting him on his career in exercise physiology and its application to clinical problems.

Among his many scientific contributions, Dr Wasserman is probably most widely known for work related to the lactic acidosis of exercise. That blood lactate concentrations were elevated during strenuous exercise had been recognized since the early 1900s. Description of the lactate profile as nonlinear, with elevations beginning at a critical, or threshold, level of exercise can be dated to as early as 1930 (1). There was thus a basis in the early 1960s for the young Dr Wasserman to postulate that the threshold for lactate elevation would occur at a lower level of exercise if oxygen delivery were impaired by cardiovascular disease, and that this could be meaningfully quantified from analysis of pulmonary gas exchange. He coined the term *anaerobic threshold* for this parameter in his 1964 report on exercise responses in cardiac patients (2). Debate about the mechanisms of lactate accumulation during exercise and the use of the term

anaerobic would persist for decades after that landmark paper, but not negate the pragmatic value of anaerobic threshold and other exercise gas exchange variables in the objective assessment of disease, impairment, and prognosis.

When Dr Wasserman began to consider the evaluation of patients with heart disease, exercise stress testing with electrocardiogram monitoring was being introduced into clinical medicine. The analysis of pulmonary gas exchange from exhaled breath was in use for quantifying metabolic rate at rest and exercise in research laboratories. Measuring gas exchange was cumbersome, however, and not readily transferable to clinical settings. To more precisely resolve dynamic gas exchange responses to exercise for physiologic research, and ultimately to make the measures accessible for use by clinicians, more facile methods would be needed. After completing fellowship at CVRI and joining the Respiratory Physiology faculty at Stanford University, Dr Wasserman established what would become a long-standing collaboration with Dr William Beaver, a physicist at Varian Industries in Palo Alto. Their work included seminal papers in the field of exercise testing (3,4) and advanced technical and analytic processes for quantifying gas exchange. The development of rapidly responding gas analyzers and expanded capacity of computers for data processing allowed them eventually to realize the goal of measuring pulmonary gas exchange in real time on a breath-by-breath basis (5,6).

In a 1967 report (7) based on data from 10 healthy subjects, Dr Wasserman portrayed the interactions of metabolic, cardiovascular, and ventilatory responses to exercise as a set of interdigitating gears (Figure 1), a simple conceptual model for characterizing exercise intolerance that would be widely popularized. That same year he was recruited to establish a Respiratory and Critical Care Division at Harbor-UCLA Medical Center, where he would work for the next 5 decades. With him came Dr Brian Whipp, having recently completed his doctorate in physiology at Stanford University. The collaboration of Drs Wasserman and Whipp included key studies leading to the design of rapid

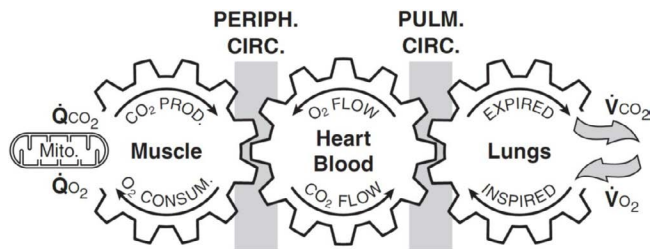


FIGURE 1. Dr Wasserman's gears presented as 3 linked systems, representing the integrated functioning of ventilation, circulation (pulmonary and peripheral circulation kept in flow by the heart), and muscle metabolism during exercise. Used with permission (11).

incremental exercise test protocols and rigorous approaches to modeling and characterizing exercise data (8–10), which provided much of the basis for the way that clinical cardiopulmonary exercise testing (CPET) is currently conducted.

By the early 1980s, interest in CPET was expanding more rapidly than facilities and expertise to perform it. In response, Dr Wasserman and colleagues at Harbor-UCLA established a recurring 3-d course for physicians and scientists on the principles of exercise testing, and not long thereafter published a text integrating their foundational research with their experience in clinical CPET (11). The course continues to be conducted regularly and has been replicated around the world (Figure 2); the text has been translated into multiple languages and was recently released in its 6th edition (12).

Dr Wasserman mentored hundreds of young investigators and physicians in the tradition of his own mentorship, formed collaborations that crossed geography and scientific disciplines, and encouraged development by the commercial sector of instruments essential to making CPET available to clinicians. With this network of colleagues, he published

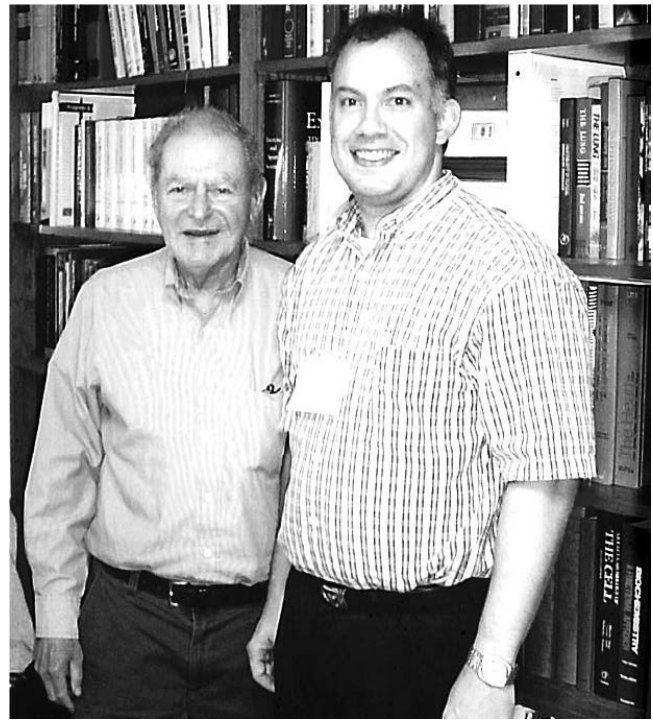


FIGURE 2. Dr Wasserman and the journal's Editor-In-Chief during a CPET course at Harbor-UCLA in the early 2000s.

close to 400 scientific papers, as well as books, chapters, and monographs on topics ranging from the control of ventilation to novel treatments for rare pulmonary conditions, as well as exercise function in health and chronic disease states. His legacy as a physician-scientist includes a body of research motivated by the goal of improving patient care and a record of clinical teaching focused on the primary importance of understanding normal physiology in order to identify and treat pathophysiology.

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