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OBITUARY

Ewald R. Weibel (1929–2019)

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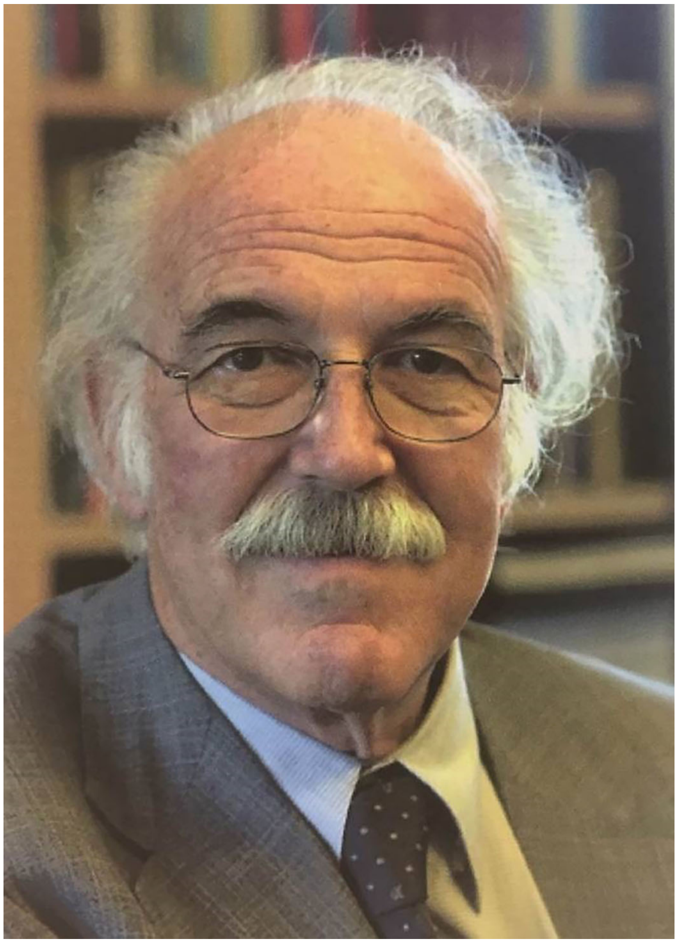

Ewald R. Weibel passed away on 19 February, aged 89. His remarkable intellect remained intact even as his physical condition worsened. He continued to be fully engaged scientifically at the time of his death, in close professional contact with his longtime associates Connie Hsia (University of Texas, Southwestern Medical Center, Dallas) and Matthias Ochs (Charité, Berlin). It will come as no surprise to those who knew him that he was preparing his ultimate research paper, finishing the draft for its Introduction just 2 weeks before his final hospitalization.

Weibel's journey from his childhood home in Zurich to membership into the National Academy of Sciences was an interesting one with many unexpected turns. He came from a modest family background; his father was a typewriter mechanic. It was a financial stretch for the family to have their son studying medicine, which he did with a state stipend. When Weibel graduated, he had to find employment, as interns then rarely received a salary during their first 2 years of clinical training. Little did he know that this 'outside employment' would set a path on which he would remain for his entire scientific career. His job in pathology was a mandate to study the anastomosing vessels between the bronchiolar and the pulmonary circulation. In an ingenious experiment, he showed that the particular structure of these arteries, with longitudinal muscle strands in the intima, could be attributed to the stretch to which these arteries were subjected during ventilation, unrelated to their anastomosis function. This work earned him a 2 year fellowship jointly funded by the Swiss Academy of Medical Sciences and the National Institutes of Health. His intention was to study the physiology of the collateral circulation in the lung in André Cournand's laboratory at Columbia University (Cournand had received the Nobel Prize in Physiology just previously in 1956). Newly wed to his supportive wife Verena, they travelled to New York by ship. After a short stint in Avriell Liebow's laboratory at Yale, and after a successful seminar at Columbia, Weibel realized his dream and joined Cournand's team. As one might surmise, Nobel Laureates are outstanding 'talent scouts', and Cournand immediately offered him a laboratory and generous resources with only one requirement: '*Do anything on the structure of the lung that is of interest to physiology*'.

As Weibel started his work in Cournand's laboratory, he made a crucial acquaintance. In September 1959 he met Domingo Gomez, a brilliant exiled Cuban biophysicist also working in Cournand's laboratory whose interest was modelling gas exchange in the human lung from first principles. Together, they soon realized that to do realistic modelling of gas exchange, they must rely on quantitative data on the anatomical structures relevant for gas exchange. As the lung's surface area is only anatomically accessible on thin sections of lung tissue, a serious problem had to be solved: how to make accurate estimates of physiologically relevant structural properties in three dimensions from measurements made on tissue sections in two dimensions. Aspects of this problem had previously been solved for metallurgy and geology, but these techniques had not been applied in biology. So together with Hans Elias, Weibel was an early key promoter of a branch of probabilistic geometry later to be named 'stereology' or 'morphometry'. Stereological estimates of some quantitative parameters of the lung and a model of the branching pattern of the alveolar tree led Weibel and Gomez to publish a landmark paper on the architecture of the human lung.

However, it soon became clear that the resolution of light microscopy was simply not good enough to resolve the intricate structure of the interface between the air space and the erythrocyte in the lung capillary to realistically model lung diffusion capacity from structural quantities. In 1961, Weibel realized that he needed the resolution power afforded by electron microscopy to obtain the structural estimates needed for physiologically relevant modelling.

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Fortunately for Weibel, Cournand established contacts with George Palade at Rockefeller. Palade was a pioneer of electron microscopy who went on to receive the Nobel Prize in Physiology in 1974 for his contributions in laying the structural foundation for cell biology. Weibel was thus able to learn electron microscopy, the then cutting-edge tool of biology, at Palade's laboratory. The resolution of electron microscopy allowed for structural measurements of the last step of the oxygen transfer from the air in the alveoli, through the tissue barrier and the plasma space into the red cell, as needed for the modelling efforts of Gomez.

While at Rockefeller, Weibel came across peculiar tubular structures that he found in endothelial cells of a rat lung but also in endothelia of other tissues. These structures had not been described before, and with Palade he published his findings. Today these structures are known as ubiquitous markers of endothelial cells under the name of 'Weibel–Palade bodies'. Much later, in 1982, it became known that the Weibel–Palade bodies contain, amongst other things, the von Willebrand factor, which is a key component of coagulation.

By 1962, Weibel, his student visa expired, was forced to return to Switzerland. The University of Zurich offered him an assistant professorship with the task to set up the first electron microscopy unit. It was not long before Swiss universities were competing for Weibel's skills and intellect, and in 1964, at the age of 35, he accepted an offer to become the Director of the Department of Anatomy of the University of Bern. With considerable financial support of the canton of Bern, Weibel was tasked to establish a cutting-edge institution for quantitative structural research. This gamble by the University of Bern paid off big time, as this institute became the reference laboratory for quantitative structural analyses on the microscopic and electron microscopic level world-wide and is known as the nurturing ground for the development of stereology. Weibel's love for stereology had much to do with the fact that stereological measurement techniques are derived from first principles and, when done correctly, allow for obtaining unbiased estimates for volumes, surfaces, lengths and numbers of structures or compartments in biological samples. Stereological techniques are basically the only unbiased approach to assess biological properties, as the stereological tools are derived from mathematical principles. Any other assay that is used today in biology (be it biochemical or molecular) is, by necessity, biased.

The main focus of the experimental work at Weibel's laboratory continued to be the gas exchange apparatus. He was keenly interested in the potential malleability of the pulmonary gas exchanger with exercise and hypoxia but also understood the value in comparative physiology. He studied the lungs of very small mammals, such as the 3 g Etruscan shrew, as well as human lungs that were collected post-mortem. In various collaborations he also made his morphometric techniques available for the study of fish gills and the lungs of birds. An important finding of these studies was that in a comparative context, pulmonary diffusing capacity, as measured by morphometric techniques, scaled in direct proportion to body mass (scaling factor 1) whereas resting oxygen consumption scaled to body mass with a scaling factor of 0.75 – an apparent discrepancy.

As his pursuits grew, he never lost his interest in the nature of the Weibel–Palade bodies. So on his first sabbatical in 1975 he decided to once again join his old friend Palade, and together they used cell biological techniques to unravel the function of the tiny tubular structures in endothelia that carried his name. It turned out that this was one of the few projects that Weibel did not finish with success; a reminder of how failure is an integral part of success. Indeed, this led to a long and productive new direction.

The failure to unravel the secret of the Weibel–Palade bodies gave Weibel the opportunity to meet C. Richard ('Dick') Taylor, a Harvard University comparative physiologist who had a gift for measuring the maximum aerobic capacity ($\dot{V}_{O_2,max}$) in a number of mammalian species of different body size. The two of them decided to join forces to launch an expedition to Kenya with the aim of understanding oxygen uptake, transport and utilization across species. To do this, they measured $\dot{V}_{O_2,max}$ data on as many wild African species as possible and coupled those data with samples of lung and muscle morphometry from the same animals. This gigantic project was the start of a close friendship between Weibel and Taylor that lasted until Taylor's death in 1995. It was also the start of an extremely fruitful collaboration between Taylor's laboratory at the Concorde Field Station of Harvard University and the Department of Anatomy of the University of Bern. The collaboration resulted in more than 25 joint publications. The unique contributions of this research matched the maximal oxygen uptake of animals to their relevant quantitative structural features of the heart, the circulation and the skeletal muscle tissue. This body of work provided countless insights into the design of the entire respiratory cascade in mammals in a coherent quantitative frame and under limiting physiological conditions of $\dot{V}_{O_2,max}$.

One indisputable finding of this long collaboration was the close match between structure and function in the design of the mammalian respiratory system, linking the 'upstream' and 'downstream' steps of the respiratory cascade. Weibel coined the term of 'symmorphosis' to denote that each step of the cascade was exactly quantitatively tuned to demand: there was enough – but not too much – structure to support oxygen flow. But he also found one apparent exception to his concept of symmorphosis – namely, the lung. The analysis indicated that there was seemingly excess lung structure in large animals. This finding continued to bother him for the rest of his career and through all of his retirement. In fact, the last manuscript he was working on dealt with this problem and the potential effect that shorter alveolar duct lengths in small animals could have on the condition of oxygen transfer between the alveolar air space and erythrocytes.

Weibel will be remembered as an outstanding scientist. His articles and books cover three main areas: lung structure and function, stereology, and the design of the respiratory system. For his work, he has received a number of prestigious academic prizes such as the Marcel Benoist Prize, the Anders Retzius Medal and the Purkinje Gold Medal. He also served in many academic functions such as Rector of the University of Bern, President of the Swiss Academy of Medical Sciences and President of the International Union of Physiological Sciences. Above all, Weibel was an inspiration to all who had the chance of working with him. He had a piercing mind, he loved the academic battle and he hated any kind of dishonesty. It was important for him to follow and foster the career of his many collaborators. Throughout his career and as a head of the Department of Anatomy, he shouldered a full teaching load. He was a brilliant and engaging role model for all medical students and he remained proud of his first academic vocation as a medical doctor. He will be sorely missed. Ewald Weibel leaves behind his wife Verena, whom he had lovingly cared for during the final years of his life.