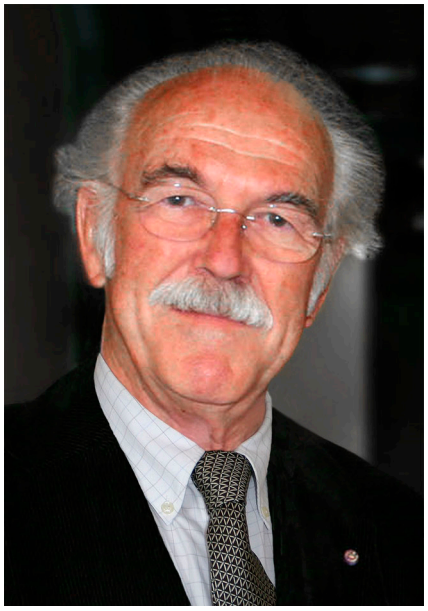
Ewald Weibel: An organelle of his very own, and more

Weibel built his career using electron microscopy to study cells, tissues, and biological systems.

Weibel-Palade bodies are membrane-bound, rod-shaped organelles found exclusively in endothelial cells. These structures were utterly mysterious when Ewald Weibel, working in George Palade's laboratory, first described them in a seminal 1964 *JCB* paper (1). But it's now known that their distinctive shape is imbued by tightly wound strands of a protein called von Willebrand Factor, which is released from Weibel-Palade bodies to assist with blood clotting when endothelia are injured.

By 1962, when he discovered the organelles that would bear his name, Weibel had already perfected several new microscopy techniques (2, 3) essential to understanding tissue and cellular organization and composition (4–6), which are still in use today. His later work continued to break new ground on how biological systems are organized to meet metabolic needs (7). Now retired for 18 years, Weibel graciously agreed to discuss with us the story of his life and career.



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Ewald Weibel

A GOOD BEGINNING

What was it like growing up in Switzerland during World War II?

We followed what was happening on the radio every day, but of course we were observing it from the outside because Switzerland was not involved in the war. There were shortages of almost everything, even in Switzerland. But I was only ten years old when the Second World War started, so I was really too young to fully understand what was happening.

I was born and grew up in a small village near the town of Aarau. My mother was a seamstress and my father a typewriter mechanic, so I did not come from an academic background, but I went to the state college in Aarau, the same school Albert Einstein had attended 50 years before. The teachers there were very fond of challenging their students, and that was how I first became interested in science and the investigative spirit. My classmates and I were very receptive to this kind of teaching, and, in fact, out of the 25 people in my class, seven went on to university careers and two were elected to the US National Academy of Sciences: myself and Werner Arber, who would win the Nobel Prize in 1978.

Even after more than 60 years, we all still have a strong sense of camaraderie; every year in May we have a class meeting—those of us that still survive.

> "What I had thought was a stick-like piece of dirt or dust was in fact something biological."

You trained as an MD…

Yes, because as a doctor I would be able to earn my bread! After medical school in Zurich, I intended to become a surgeon, but first I had to find a job to support myself and my young wife. So I took a paid teaching fellowship in the anatomy department and began to research some special vessels believed to regulate the blood flow between the high-pressure bronchial artery and the low-pressure pulmonary artery in the lung. I was a "young Turk" then, with little respect for authority. I felt that this theory was wrong and did a little experiment that proved it incorrect—which then gave me a chance to obtain, in 1958, a fellowship to go abroad and continue my studies on bronchial arteries at Yale.

A year after I came to the United States, André Cournand and Dickinson Richards recruited me to work with them at Columbia University to "do anything on the structure of the lung that was of interest for physiology." There, I met Domingo Gomez, a Cuban refugee, who worked on a theoretical model for gas exchange in the lung and asked me questions about how many alveoli there were or how large the lung's inner surface was. The problem was how to obtain such data. Gas exchange takes place at microscopic structures, the capillaries, but they're housed in a huge organ. When we want to look at these structures with a microscope, we can only examine a tiny sample, a thin, two-dimensional section. So here was a good challenge: could we extract accurate information from a two-dimensional section that represents a three-dimensional structure? To do that, we developed mathematical methods that were partly used in materials science, methods that were later called stereology.

KEEN EYE FOR DETAIL

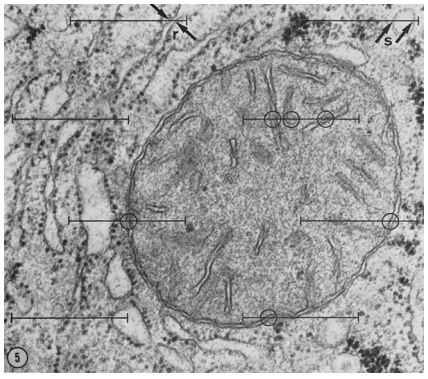
How did you come to make the first observations of Weibel-Palade bodies?

In the mid-1950s, George Palade and Keith Porter at The Rockefeller University had developed the methods for using electron microscopy in biology. In 1961, I had reached the limit of what I could do in my lung studies with light microscopy, because the actual step of gas exchange occurs across a barrier of tissue that is a fifth of one micron thick. I needed electron microscopy and convinced Cournand to send me to George's lab to be trained in this new method.

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

In February of 1962 I was looking for capillaries in rat lungs when I came upon the section of a small pulmonary artery that was contracted, and I noted that the endothelium contained some strange, large structures. I could not really interpret what I saw, so I decided to take a picture and have a closer look, even though the section was not very nice: it was dirty and had a scratch. When I enlarged that picture, I saw that what I had thought was a stick-like piece of dirt or dust was in fact something biological—a rod-shaped structure in the endothelial cytoplasm. I knew from my experience with stereology that it was highly unlikely to find a section that cut across a rod-shaped structure lengthwise from one end to the other. It would be more likely to see transverse or oblique sections, so I went looking for those and indeed found dozens of them.

When I showed my micrographs to George, he was surprised; he'd never noticed anything like this before. We went into his files and looked at his pictures of blood vessels in different organs and species and found these structures in every artery. But of course we still had no idea what they were, so we described them simply as new cytoplasmic components of endothelial cells.



Characteristics of submicroscopic structures can be inferred using a statistical technique called stereology (5).

It took another 20 years to find out what they were for…

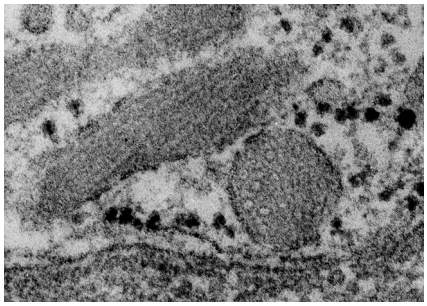
By the time I first observed what would later be called "Weibel-Palade bodies," I had already decided to go back to Switzerland. I accepted an assistant professorship at the University of Zurich to set up the first electron microscopy lab at the university and a few years later moved to the University of Bern as professor and chairman of the Institute of Anatomy. My research funding was justified by the work I was doing on the lung, so I did not have many resources to devote to "my" mysterious granules. Some of my thesis students working on the problem made some important early findings, which suggested that these structures had something to do with blood clotting. This was not my field of expertise, and I couldn't find anyone who was interested in working on it, so that was as far as we could take it at the time.

> "The stereological methods I had developed for the lung could immediately be applied to cell biology."

A FULL LIFE

What did you work on after that?

My work focused on quantitative structure-function studies on the lung. But many of the things I worked on throughout my career touched on cell biology. I also realized, thanks to my training with George Palade, that the stereological methods I had developed for the lung could immediately be applied to cell biology. For example, we could ask questions such as how many mitochondria are there in the cells, and is this different in tissues or organisms with different energy requirements? One of my students found a direct relationship between maximum oxygen consumption and the amount of mitochondria in human leg muscles. That, in turn, led us to study larger questions about how the entire lung-blood-muscle system is built to acquire, transport, and use oxygen—what we called systems biology, although this isn't what I think most cell biologists mean by "systems biology" these days. [Laughs]



A micrograph showing Weibel-Palade bodies from the original 1964 paper (1).

Our real breakthrough on this came when C. Richard Taylor from Harvard began collaborating with us. Together we came up with the theory of symmorphosis, which postulates that structures are designed commensurate to the functional needs: "enough but not too much."

Are you still active in research?

I'm professor emeritus at the University of Bern. I don't have a lab anymore, just a desk and a bookshelf. But of course the game goes on. I have a number of collaborations, as people still want my expertise in stereology and in systems analysis, for bringing lung morphometry to the new in vivo imaging modalities such as high-resolution computer tomography or MRI, for example. And then, of course, I enjoy life together with my wife in a wonderful house and garden overlooking the Alps, and I cultivate a little vineyard, to make a bit of my own wine. That's my life now!

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