OBITUARY

George Palade 1912–2008

George Emil Palade, universally hailed as the founder of modern cell biology for his many discoveries and insights into the structure and function of eukaryotic cells, died on 7 October at the age of 95. He was pre-eminent among a small group of scientists who, in the mid-twentieth century, first used the electron microscope to study cell structure, developed and refined techniques necessary to observe cells, and introduced methods that permitted the isolation and biochemical characterization of many cell structures.

Palade's seminal discoveries transformed cell biology from a largely descriptive discipline into a molecular science. He was awarded the Nobel prize in Physiology or Medicine in 1974, which he shared with Albert Claude and Christian de Duve, "for their discoveries concerning the structural and functional organization of the cell".

Palade began his discoveries at the Rockefeller Institute, where he worked for twenty-eight years. He then moved to Yale University School of Medicine, where, from 1973-1990, he assembled a new generation of brilliant cell biologists and laid the basis for a Department of Cell Biology. Finally, at the University of California in San Diego, he continued his work, established a division of Cellular and Molecular Medicine and served as the first Dean of Scientific Affairs until his retirement in 2001.

Palade was born 15th November 1912 in Jassy, Moldavia, the easternmost province of Romania. He studied medicine at the University of Bucharest and in 1946, went to the USA for further study. There he joined the laboratory of Albert Claude at the Rockefeller Institute, who with Keith Porter and Ernest Fullam had previously made the first observations of intact cells with the electron microscope and discovered the existence of an extensive 'lace-like reticulum'. Using centrifugation techniques, Claude had also succeeded in obtaining subcellular fractions, including one containing tiny particles he called 'microsomes', but whose precise origin was yet to be determined.

Palade's first breakthrough was the development, in collaboration with George Hogeboom and Walter Schneider (two of Claude's associates) of the now commonly used medium containing sucrose to preserve the integrity of organelles during tissue homogenization and fractionation. The 1950s witnessed a period in which pioneering electron microscopists, including Palade and Porter, feverishly endeavoured to improve preparation procedures applicable to solid tissues that could yield the ultrathin sections required for electron microscopy. In this period, Palade and Porter were unrivalled in the number of important new observations they made with the electron microscope.

In 1953, Palade first described the internal structure of mitochondria, including the infoldings of the inner membrane, which he called cristae mitochondriales, and in 1954, with Porter, described in various cell types and tissues the invariable presence of the 'endoplasmic reticulum' (ER), the lace-like system of interconnected tubular or cisternal cavities bound by a membrane, which had been first observed in intact cultured cells. Soon after, Palade made the momentous discovery of the ribosome, the protein-synthesizing organelle. He recognized that ribosomes exist free in the cytoplasm or attached to the ER membranes, often arranged in patterns that we now know to represent polysomes (sets of ribosomes translating a single RNA molecule).

Palade's genius, however, was his masterful combination of electron microscopy with cell fractionation and biochemical analysis, which reached its climax with the demonstration of the functional connectivity, mediated by vesicular carriers, of the different membrane-bound compartments of the cell that constitute the secretory apparatus.

In 1955, Palade recruited Phil Siekevitz to the Rockefeller Institute, with whom he undertook the task of characterizing the microsomal fraction, which they showed consisted of closed membrane vesicles derived from fragmentation of the endoplasmic reticulum. They were able to prepare purified ribosomes, free and membrane-attached, and to show that secretory proteins are exclusively synthesized in the latter and accumulate in the lumen of the ER before they appear in secretory granules.

Palade's studies on the secretory process culminated in his classical work with James Jamieson — first his student and later, for many years, close associate — using an *in vitro* pulse-chase labelling protocol to track the fate of radioactive proteins synthesized in pancreatic tissue slices. Jamieson and Palade showed that after accumulating in the ER, secretory proteins were subsequently transferred to the Golgi apparatus and then concentrated in developing secretory granules. This was the first demonstration that transport from the ER to the Golgi apparatus takes place by vesicular carriers and that the Golgi apparatus serves as a way-station for the passage of proteins to post-Golgi destinations. These findings opened a new, still thriving, field of research: that of intracellular protein traffic.

I worked in Palade's laboratory, using microsomes to demonstrate that nascent polypeptides, during the course of their elongation, are directly inserted into the ER membrane to be discharged upon completion into the microsomal lumen. This work sparked ideas on how peptide segments within newly synthesized polypeptides could serve as signals that determine the subcellular destination of proteins. These studies inspired the work of Gunter Blobel who won the Nobel Prize in 1999.

There is virtually no cellular membrane system in differentiated eukaryotic cells that did not attract Palade's attention and whose illumination he did not contribute to enhance. His work on a variety of membrane systems extended the role of the ER to the biogenesis of membranes and led to his formulation of the concept that new membranes are not formed *de novo*, but by expansion of pre-existing ones.

Of particular interest to Palade were the mechanisms that control capillary permeability, which he studied in various systems. With his former associate and later, wife, Marilyn Farquhar, he also provided the foundational characterization of junctional complexes that hold together epithelial cells.

Palade was a formidable scientist and a rigorous scholar. He was a man of exceptional qualities, with a wonderful aesthetic sense and a love of art, history and literature. He was kind, generous and always concerned with the welfare of others. He attracted the admiration and friendship of those who had the privilege of working with him. Indeed, he was one of the most loved and admired biologists of the twentieth century.

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