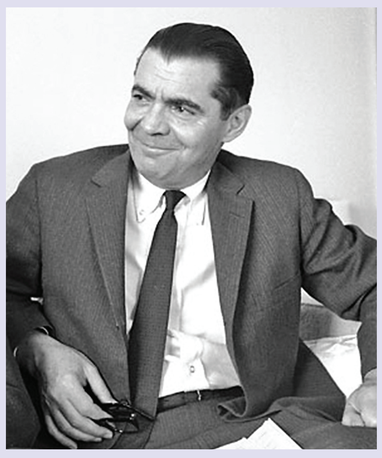
George Palade, 1912-2008

Biography

George Palade was born in November, 1912 in Jassy, Romania to an academic family. He graduated from the School of Medicine of the University of Bucharest in 1940. His doctorial thesis, however, was on the microscopic anatomy of the cetacean *delphinus Delphi*. He practiced medicine in the second world war, and for a brief time afterwards before coming to the USA in 1946, where he met Albert Claude. Excited by the potential of the electron microscope, he joined the Rockefeller Institute for Medical Research, where he did his seminal work. He left Rockefeller in 1973 to chair the new Department of Cell Biology at Yale, and then in 1990 he moved to the University of California, San Diego as Dean for Scientific Affairs at the School of Medicine. He retired in 2001, at age 88. His first wife, Irina Malaxa, died in 1969, and in 1970 he married Marilyn Farquhar, another prominent cell biologist, and his scientific collaborator. He died October 7, 2008, aged 95, leaving his wife, two children, and two stepchildren.



The Founding of Cell Biology

The discipline of Cell Biology arose at Rockefeller University in the late 1940s and the 1950s, based on two complimentary techniques: cell fractionation, pioneered by Albert Claude, George Palade, and Christian de Duve, and biological electron microscopy, pioneered by Keith Porter, Albert Claude, and George Palade. For the first time, it became possible to identify the components of the cell both structurally and biochemically, and therefore begin understanding the functioning of cells on a molecular level. These individuals participated in establishing the *Journal of Cell Biology*, (originally the *Journal of Biochemical and Biophysical Cytology*), which later led, in 1960, to the organization of the American Society for Cell Biology by Keith Porter.

Major contributions

Specimen preparation for electron microscopy

The first good EM images of cells were obtained by Keith Porter and Albert Claude at Rockefeller, with the help of Ernest Fullam and the RCA EMB at Interchemical Corp. (Porter *et al.*, 1945). The cells were osmium-strained whole-mounts. Initially, it was frustrating that cells in tissue could not be adequately prepared. However, by the early 1950s, methods were developed that allowed thin sections of cells to be examined. There were two critical components. The first was improved fixation, and Palade made an important contribution by carrying out exhaustive tests to establish the use of buffered osmium as a primary fixative (Palade, 1952a). The second important advance was in cutting sections thin enough for high-resolution EM, and this was also developed at Rockefeller, by Porter and Joseph Blum (and in parallel in Sweden by Sjöstrand). This opened the initial golden age of biological electron microscopy, with numerous important discoveries being made in quick succession.

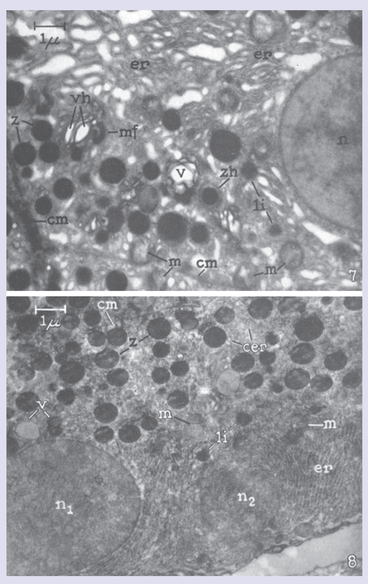


Figure 1. (From Palade, 1952a) Pancreatic exocrine cells fixed in 1% OsO4. The fixative was in distilled water for the top image, and buffered at pH 7.4 with acetate-veronal buffer for the bottom image. OsO4 was a common fixative in those days, but Palade was the first to find that the high acidity of the unbuffered solution caused obvious artifacts.

Ribosomes

Palade discovered and described small granular components, now known as ribosomes, covering the outside of the membranes (Palade, 1955), and he showed that these corresponded to the "microsomes" from cell fractionation. Subsequently, along with other groups, it was shown that the ribosomes carry out the protein synthesis in the cell.

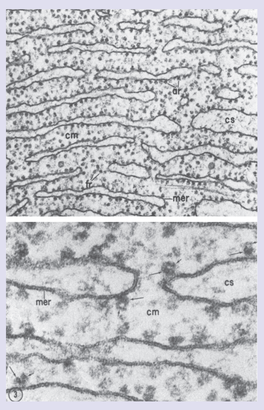


Figure 3. (From Palade, 1975) Rough endoplasmic reticulum (ER) and ribosomes from a pancreatic exocrine cell. In the late 1950s, by combining EM and ultracentrifugation, Palade identified the particles on the ER to be sites of protein synthesis, later named ribosomes. In the lower image, the large (long arrow) and small (short arrows) ribosomal subunits could be identified.

Membrane biogenesis

Working with endoplasmic reticulum of animal cells, and thylakoid membranes of Chlamydomonas reinhardtii Palade's group demonstrated that membranes are not assembled *de novo*, but existing membranes are extended by the random addition of new membrane proteins, and that turnover of these membrane proteins occurs (Palade, 1983). Later, they studied factors influencing the growth of blood vessels within tumors (Roberts and Palade, 1997).

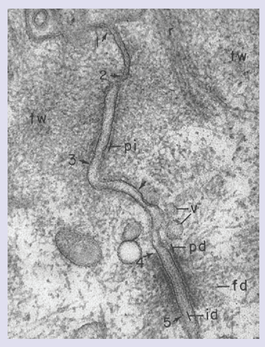


Figure 5. (from Farquhar, 1963) Another important focus of Palade's research, epithelial cell junctions, was shared with Marilyn Farquhar . This image shows three different types of junctions in the epithelium of rat intestinal mucosa: Arrows 1 to 2, tight junction (*zonula occludens*); arrow 2 to 3, intermediate junction (*zonula adherens*), and arrows 4 to 5, desmosome.

Cell fractionation

When Palade first arrived at Rockefeller, he worked on cell fractionation and biochemical analysis. When Claude returned to Belgium in 1949, Porter and Palade joined forces in electron microscopy, but Palade returned to cell fractionation, and refined the technique by introducing use of the sucrose-gradient ultracentrifugation technique (Sabatini *et al.*, 1966). This was a very important advance that enabled the biochemical study of specific cell organelles, perfectly complementing the new high-resolution cellular structure now seen by electron microscopy. This formed the cornerstone of Palade's work, an integrated understanding of the cell at the level of organelles and macromolecules, and continued throughout his career (e.g. Howell and Palade, 1982; Saucan and Palade, 1994)

The endocytic pathway

In the 1960s, Palade and colleagues identified the route that secretory proteins take, from the site of synthesis by the ribosomes on the outside of endoplasmic reticulum cisternae, across the membrane into the lumen, and then into the Golgi complex. Later, the combination of cell fractionation procedures, EM autoradiography, and immunocytochemical procedures led to the identification of the individual compartments along the way to extracelluar secretion. (Palade, 1975)

The transcytotic pathway

With Marilyn Farquhar (whom he married 1970), Palade studied transport across vascular endothelia. The basement membrane of the capillaries in renal glomerlui were found to act as a filtration barrier for molecules 10 nm for larger (Farquhar et al., 1961). A variety of junctional complexes (Farquhar and Palade, 1963) and endocytic processes involving plasmalemmal vesicles and caveolae were found as passageways for large molecules across the endothelium (Predescu and Palade, 1993).

Mitochondria

The new preparation methods allowed study of organelles in detail, and Palade was first to show the structure of the mitochondria (Palade, 1952b), and was even able to visualize what later was identified as the ATPase molecules.

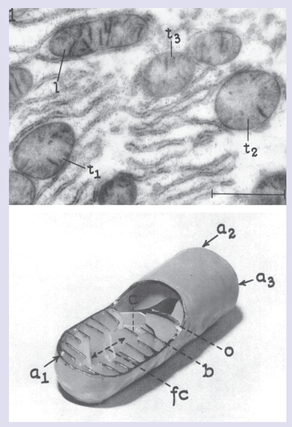


Figure 2. (From Palade, 1952b) Rat liver mitochondria in transverse (t) and longitudinal (l) sections. The model was constructed by synthesizing the longitudinal views (section a1-a2) and the transverse views (a2-a3). A crista that would appear free in a section is marked by (c), a branching crista is marked by (b), and a thick lamella oblique to the sectioning plane is shown at (o). A central free channel (fc) is indicated. This model persisted well into the 1990s, when electron tomography showed that the cristae are usually tubes, rather than plates.

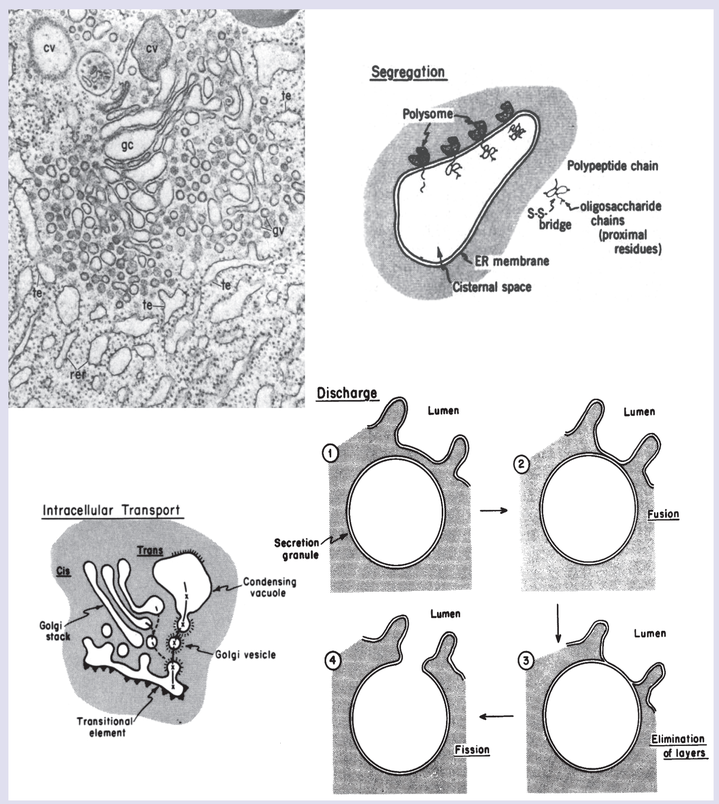


Figure 4. (From Palade, 1975) Palade's major focus was the synthesis and transport of proteins in the cell. His favorite model was the pancreas exocrine cell, studying the structure and function of the Golgi, ER, and the variety of vesicles found there (upper left). The three diagrams, from his Nobel lecture, depict the steps of Segregation, Intracellular Transport, and Discharge of secretory proteins.

The Nobel Prize

The 1974 Nobel prize in Physiology or Medicine was shared by Palade, Albert Claude and Christian de Duve for their discoveries concerning "the structural and functional organization of the cell". The prize credited the winners with for the creation, in large part, of the subject of Cell Biology. Specifically, Albert Claude for having the first "glance" of cell ultrastructure, and his early work on cell fractionation; Christian de Duve for his extensive work with cell fractionation, and the discovery of the lysosome; and Palade for perfecting biological electron microscopy and discovering the ribosome.

Figure 6. Obverse of the Nobel Prize in Physiology or Medicine.

Here is an except of Palade's banquet speech after the Nobel ceremony:

"For a scientist, it is a unique experience to live through a period in which his field of endeavor comes to bloom - to be witness to those rare moments when the dawn of understanding finally descends upon what appeared to be confusion only a while ago - to listen to the sound of darkness crumbling.

Claude, de Duve and I have lived through such a period and have already enjoyed the intimate rewards that are part of this rare experience. Now, when we are singled out for this highest of all scientific prizes, we feel that the new distinction acknowledges beyond us, beyond our personal achievements, the rebirth of our field of knowledge and the vistas it has opened for the medicine of tomorrow. We accept the distinction with the deepest gratitude."

Figure 7. The 1974 Nobelists in Physiology or Medicine.

Other awards

Member of the National Academy of Sciences USA (from 1961)
Lasker Award (1966)
Gairdner Special Award (1967)
Hurwitz Prize - shared with Albert Claude and Keith Porter (1970)
National Medal of Science USA (1986)

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