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The Legacy of a Founding Father of Modern Cell Biology: George Emil Palade (1912-2008)

Suzana M. Zorca, MD,a and Cornelia E. Zorcab*

aDepartment of Anesthesiology, Yale-New Haven Hospital, New Haven, Connecticut, and
bDepartment of Genetics, Yale School of Medicine, New Haven, Connecticut

George Emil Palade’s scientific contributions significantly advanced the field of modern cell biology. He pioneered a multidisciplinary approach, combining cell fractionation, biochemistry, and electron microscopy, which led to the identification of the ribosome as the site of protein synthesis and elucidated the eukaryotic secretory pathway. For these accomplishments, Palade, along with Albert Claude and Christian de Duve, won the 1974 Nobel Prize in Physiology or Medicine. This article provides an overview of Palade’s seminal research in the context of the early developments in the field.

INTRODUCTION

George Emil Palade (Figure 1) was born in Iasi, Romania, in 1912 and was the son of a philosophy professor and an educator. Early in his life, he chose to pursue medicine because of its focus on the “tangibles and specifics” [1] of physiology and the scientific method. However, his interests were remarkably diverse, and he inherited a deep-seated respect for philosophy and rational inquiry from his early upbringing. At the age of 18, he matriculated at the University of Medicine of Bucharest and in 1940 completed his doctoral thesis on the “microscopic anatomy” of the dolphin nephron [1]. In studying this unique topic, he developed an understanding of the functional adaptation of mammals to marine life. This early academic work occurred during the politically tense years leading up to World War II. Recalling the social and political turmoil sweeping through Europe in the pre-war era, Palade noted, “. . . the continent was torn apart by all kinds of ideological movements. This state of insecurity had [a] significant impact during my studies” [2]. The young Palade served in the medical corps *To whom all correspondence should be addressed: Cornelia E. Zorca, Department of Genetics, Yale School of Medicine, 300 Cedar Street, P.O. Box 208011, New Haven, CT 06520; Tele: 203-785-5383; Email: cornelia.zorca@yale.edu.

†Abbreviations: NYU, New York University; EM, electron microscopy; RNA, ribonucleic acid; ER, endoplasmic reticulum; RNP, ribonucleoprotein; ATP, adenosine triphosphate; UCSD, University of California, San Diego.
of the Romanian Army. Upon his return from the war, he became a faculty member of the Institute of Anatomy at his alma mater and remained there until 1946.

In 1946, Palade moved to the United States to pursue postdoctoral studies in the laboratory of Robert Chambers at New York University (NYU). Shortly thereafter, Palade met Albert Claude after a lecture Claude gave at NYU concerning electron microscopy. Palade became intrigued by the potential of this technique to reveal the cellular and sub-cellular organization of tissues and joined Claude at the Rockefeller Institute for Medical Research in the fall of 1946 [1]. Together with Claude, George Hogeboom, and Walter Schneider, Palade developed the sucrose method for tissue fractionation and subsequently optimized tissue fixation with buffered osmium tetroxide for electron microscopy (EM) structural studies [1,3]. These two advances, described in more detail below, were instrumental in Palade’s landmark discovery of “…a small particulate component of the cytoplasm (later called ribosome)” [1].

As he progressed from Assistant Professor to head of the Laboratory of Cell Biology at the Rockefeller Institute, Palade’s research focus shifted toward elucidating the pathway of protein synthesis and secretion. With a unique “…ability to link the most disparate observations into a coherent and testable working hypothesis” [4], he pursued critical questions involving sub-cellular tissue organization and protein trafficking. Effortlessly, he passed on his passion for in-depth scientific dissection of physiological pathways to numerous students and postdoctoral fellows [4]. His work on the secretory pathway constitutes a central component of the field of modern cell biology.

**EARLY TECHNICAL ADVANCES IN MICROSCOPY AND SUBCELLULAR FRACTIONATION**

Just a few years before Palade joined Claude at the Rockefeller, Claude had used differential centrifugation to separate intracellular components from guinea pig liver homogenized in saline or water [3]. By subjecting the liver tissue homogenates to sequential high-speed centrifugation steps, Claude isolated three morphologically distinct fractions: a large granule fraction consisting of mitochondria, a ribonucleic acid (RNA)-rich microsome fraction, and a soluble fraction [3,4]. Palade further developed this tool by using hypertonic sucrose for homogenization and cell fractionation. His approach improved the preservation of organelle morphology compared to the use of saline or water, which led to aggregation and swelling [1,3]. Furthermore, sucrose-gradient centrifugation (based on density differences of sub-cellular components) facilitated the isolation of increasingly pure cell fractions.

When Palade first began this work, electron microscopy was still in its infancy. Improvements in microtomy and embedding yielded sections of suitable thinness, but the fixation procedures used at that time often led to precipitation artifacts. Palade’s major contribution was pioneering the use of buffered osmium tetroxide as a fixative to obtain improved contrast [1,4,5]. In the 1974 Nobel Prize presentation speech, Palade is
acknowledged as “...foremost among those who developed electron microscopy further, to the highest degree of artistry” [6]. With these early technical advances, Palade proceeded to investigate the structure and function of newly isolated organelles.

A MULTIDISCIPLINARY APPROACH TO IDENTIFY STRUCTURE AND FUNCTION

The hallmark of Palade’s research approach in the mid 1950s and 1960s was the integration of cell fractionation and EM data. Philip Siekevitz and Palade first demonstrated that the “microsome fraction” consisted of fragments of endoplasmic reticulum (ER) [7,8]. Using detergent solubilization followed by centrifugation, Siekevitz and Palade subsequently found that microsome membranes consisted of ribonucleoprotein (RNP) particles [9,10]. These RNPs later became known as ribosomes. Through a series of elegant EM studies in pancreatic acinar cell preparations, Siekevitz and Palade showed that ribosomes were the sites of new protein synthesis [9]. In tracing the fate of newly synthesized proteins with radioactive amino acids, Palade and Siekevitz showed that they accumulated in microsomal vesicles [3,9]. This was the first demonstration of vectorial transport of nascent polypeptides across the ER membrane into the lumen.

TRACING THE SECRETORY PATHWAY IN THE Pancreatic Acinar CELL

Palade’s studies of protein synthesis and secretion in the pancreatic acinar cell proved to be particularly fruitful. This model cell type was ideal for these studies because it is specialized for the secretion of digestive enzymes, including lipase, amylase, and chymotrypsinogen [7]. Together with Lucien Caro and James Jamieson, Palade developed radioautography, a method that could be used in conjunction with EM to trace the movement of radioactively labeled secretory proteins from their site of synthesis to the site of release from the cell [7,11]. Specifically, Jamieson and Palade used pulse-chase labeling of secretory proteins in pancreatic tissue slices to visualize the secreted proteins as grains in EM [7,11]. Following a short pulse with radioactive amino acids, Jamieson and Palade monitored the grains over a chase-time-course as they sequentially moved from the ribosomes of the rough ER to the Golgi complex and then to zymogen granules before reaching the plasma membrane.

These results demonstrated for the first time the role of the Golgi complex in protein trafficking [11,12]. Secondly, they showed that proteins were transported in vesicles from one cellular compartment to the next, without mixing with the cytoplasm [7]. In addition, they demonstrated that intracellular protein transport was adenosine triphosphate (ATP) dependent and that, in its absence, secretory proteins remained trapped in the rough ER [7,13]. Furthermore, Palade, Jamieson, and their coworkers demonstrated that these principles of protein transport were universally applicable to other cell types [7].

THE LATER YEARS

Palade remained at the Rockefeller until 1973, when he moved to Yale University because of “[his] belief that the time had come for fruitful interactions between the new discipline of Cell Biology and the traditional fields of interest of medical schools, namely Pathology and Clinical Medicine” [1]. He established and chaired the Section of Cell Biology and was Sterling Professor of Cell Biology from 1975 to 1983 [5]. He remained at Yale until 1990, when he moved to the University of California, San Diego (UCSD), where he founded the department of Cellular and Molecular Medicine and served as the Dean for Scientific Affairs at the School of Medicine [5].

For his seminal contributions to the elucidation of secretory pathways and establishing the early foundations of cell biology, Palade shared the 1974 Nobel Prize in Physiology or Medicine with Albert Claude and Christian de Duve [1]. His numerous additional honors include the Albert Lasker
Award (1966), the Gairdner Special Award (1967), the Hurwitz Prize (1970), and the National Medal of Science (1986), presented by President Ronald Reagan [5]. He was a member of the Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences [1,5].

In his honor, a lectureship recently was established at Yale School of Medicine as a platform for renowned national and international scientists to share their specific expertise on diverse topics in cell biology. The inaugural “George E. Palade Memorial Lecture in Cell Biology” was delivered in April 2010 by the well-known cell biologist Marilyn G. Farquhar, George Palade’s widow, his long-standing scientific collaborator and Distinguished Professor of Molecular and Cellular Medicine at UCSD.

Three years ago, Palade passed away at the age of 95 in Del Mar, California [5]. His lasting scientific legacy, acknowledged together with Claude’s and de Duve’s in the Karolinska Institute press release, was “... the creation of modern Cell Biology” through their discovery of “the structural and functional organization of the cell” [6]. As a faculty member at the Rockefeller, Yale, and UCSD and as a member of the advisory panel to the director of the National Institutes of Health, Palade worked tirelessly to infuse cell biology into other disciplines, driven by the notion that “cell biology . . . makes possible a century-old dream: that of analysis of diseases at the cellular level, the first step toward their final control” [14]. Current generations of scientists are fortunate to benefit from and to carry forward this legacy.

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