George Palade

A Man for All Seasons: Reflections on the Life and Legacy of George Palade

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Abstract

In this perspective, I review the scientific career of George E. Palade, the man many consider to be the father of cell biology. Palade's scientific contributions spanned more than 50 years (from the late 1940s to 2001) and were amazingly diverse and fundamental. He is best known for his discovery of ribosomes, for establishing their role in protein synthesis, and for delineation of the secretory pathway. In addition to these groundbreaking contributions, he also developed basic techniques for tissue preservation and cell fractionation that allowed rapid progress during the early days of cell biology, and he and his collaborators provided the first description of the mitochondrial cristae, neuronal synapses, junctional complexes in epithelia, plasmalemmal vesicles, and Weibel-Palade bodies in endothelium, among others. He and his collaborators also contributed key experimental data to our understanding not only of protein synthesis and the secretory process but also of membrane biogenesis and vascular permeability. In addition to his scientific discoveries, he had a profound impact on the lives of many cell biologists and served the scientific community tirelessly while making major contributions to the development of cell biology in three major institutions.

Contents

THE EARLY YEARS IN MEDICINE IN ROMANIA AND ESCAPE FROM THE IRON CURTAIN

George Palade was born in Jassy, Romania, in 1912 to a family that greatly valued education. His mother was a teacher and his father, a professor of philosophy, which explains why he acquired "a great respect for books, scholars, and education early in life" (Palade 1975b). He was drawn to science and medicine and entered medical school at the University of Bucharest at the age of 18. His reputation for being an outstanding student became legendary after he obtained a perfect score in all subjects on the comprehensive high school exam as well as on all of his medical school examinations. All those who knew him were convinced that George was destined to do great things.

Very early in his career, young George was attracted to exploration rather than to medical practice. During medical school he found time to work toward a doctoral degree in the Department of Anatomy and, after graduating, decided to do his doctoral thesis on "The Urinary Tubule of the Dolphin." For his thesis work he collected kidneys of dolphins from the Black Sea and made many drawings and a three-dimensional model of the dolphin nephron, which were considered so outstanding that they remained on display in the Anatomical Museum in the medical school and for many years have inspired many generations of medical students. Many of the qualities manifested by young George are those he continued to display throughout his career—in-depth analysis of the problem under investigation, a great talent for drawing (he often sketched his own models), and especially his perpetual desire to bridge the gap between structure and function. The latter was to become the hallmark of his research.

After graduation from medical school, he went on to complete six years of clinical training in internal medicine then spent a few years as an assistant in the Department of Clinical Medicine. He served briefly as a physician in the Romanian Army during World War II. However, he gave up clinical medicine because "the discrepancy between the knowledge possessed by and that expected from medical practioners of the time made me rather uneasy" (Palade 1975b). He pointed out later that he was "not really giving up medicine, but was going back to the scientific foundation of medicine and trying to do something about the gap." Thus he moved back to the Department of Anatomy (1941–1945), where his professor, Grigore Popa, realizing Palade's potential, strongly urged him to study abroad. However, the situation in Romania took a turn for the worse after the takeover by the communists in 1944, and all private property was confiscated, many intellectuals were imprisoned, and the borders were closed. Palade realized that basic research in Romania was doomed, and he felt irresistibly attracted to explore the great scientific advances and opportunities in the outside world. Armed with several letters from Dr. Popa recommending him to labs in the United States, he was able to secretly obtain a visa and passport through the black market and literally sneaked out of Romania in the middle of the night, collected his wife and daughter waiting for him in Turkey, and sailed for New York from Casablanca at the end of 1945. It was the right decision for many reasons, as his physician friends who stayed behind were all imprisoned for many years, and upon their release, their dreams of developing their careers were crushed.

The Iron Curtain had descended on Eastern Europe, and with it progress in biological sciences in Romania and the rest of Eastern Europe was frozen in time for nearly 50 years.

LAND OF OPPORTUNITY: THE EARLY ROCKEFELLER PERIOD (1946–1961)

Upon reaching New York, based on the letter of recommendation from Professor Popa, Palade received an appointment as a visiting investigator working in the lab of Robert Chambers at New York University. While there he had the good fortune to hear a seminar

given by Albert Claude on his work in electron microscopy and was offered a position by Claude in the Cytology Department at the Rockefeller Institute for Medical Research (later renamed Rockefeller University). This was a premier opportunity because at the time [before the establishment of the National Institutes of Health (NIH)] the Rockefeller was America's leading research center and was considered the ideal place to do basic biological research. It was one of the few research centers in the United States that had considerable stable funding (due to the generosity of John D. Rockefeller) and unlimited opportunities—scientists fortunate enough to work there had ample resources and no teaching responsibilities. Thus by a stroke of good fortune, in 1946 Palade landed in the heart of this fertile environment, which he would later dub "The American Cradle of Cell Biology" (Palade 2012).

Development of Novel Methods for Cell Fractionation and Electron Microscopy

Immediately upon his arrival, George started working with two of Claude's associates, George Hogeboom and W. C. Schneider, in cell fractionation and soon developed an improved method for the isolation of mitochondria from liver (Hogeboom et al. 1948). The method introduced sucrose solutions as cell-suspension media for cell fractionation and used electron microscopy and staining reactions (Janus green) to identify mitochondria. The approach had the advantage over previous methods (involving isolation in water or saline) that it preserved mitochondrial organization and retained oxidative enzyme activity. The sucrose method was extended and applied to isolation of other cell organelles (microsomes, lysosomes, Golgi complex, secretory granules), and to this day it remains the procedure used most frequently for the isolation of mitochondria and other subcellular components (Kresge et al. 2005). When Palade had been at Rockefeller for only a few years, Claude, Hogeboom, and Schneider left for other institutions, and Murphy, the head of the lab, retired. Palade and Keith Porter were essentially orphaned, and neither was yet tenured. The president of Rockefeller, Herbert Gasser, recognized their potential and the significance of their work and stepped up to adopt them. Porter initially became head of the Cytology laboratory, although it was unheard of at Rockefeller for untenured professors to be laboratory heads. Palade started working in electron microscopy, and his next contribution was to work out an improved method for tissue preservation, which involved using Veronal-acetate buffered (pH 7.0–7.5) OsO4 solutions as a routine fixative in electron microscopy (Palade 1952). The novelty consisted simply in the use of buffer as solvent. The improvement in tissue preservation over previously used methods was striking, and this together with the introduction of plastic embedding (Newman et al. 1949), glass knives (Latta & Hartmann 1950), and the design of a new microtome by Porter & Blum (1953) facilitated the cutting of sections that were thin enough to be penetrated by the electron beam. These advances made possible the application of electron microscopy to the study of the generality of cells in tissues. Until then, electron microscopy had been restricted to thinly spread cells in culture, which severely limited the information obtained. Buffered OsO4 remained the main primary fixative until the introduction of glutaraldehyde (Sabatini et al. 1963).

Exploration of Cellular Fine Structure: Discovery of Mitochondrial Structure, Ribosomes, Specializations of the Endoplasmic Reticulum, and Synaptic Structure

The techniques mentioned above marked the beginning of the golden era in electron microscopy, as they opened up for exploration a whole new layer of biological organization that stretched from ~2500 A, the limit of resolution of the light microscope, to ~2 A, the practical limit of the resolution of the electron microscope. As his contribution to this period, Palade (1953a) described the fine

structure of mitochondria and delineated the organization of their internal cristae or "cristae mitochondriales" (**Figure 1**). He also made the momentous discovery of ribosomes, initially called "the small particulate component of the cytoplasm," or RNP particles (Palade 1955a). In collaboration with Porter, he characterized the endoplasmic reticulum (ER) in a variety of cell types (Palade 1955b, Palade & Porter 1954, Porter & Palade 1957). The ER system was originally discovered in cultured cells by Porter, Claude, and Fullam in 1945 (Porter et al. 1945). Palade and Porter described the local differentiations (rough- and smooth-surfaced parts) of this system of membrane-bound channels that pervades the cytoplasm of all eukaryotic cells, and they worked out the variety of specialized forms it assumes in many differentiated cell types. During the same period, he and Palay (Palay & Palade 1955) provided the first description of the fine structure of Nissl bodies in neurons, and out of that work came the first description of interneuronal and neuromuscular synapses. Each of these fundamental discoveries would have been considered a crucial contribution to the field and a milestone for any lab. What is truly remarkable is that they were made in one lab over the span of only five years under Palade's authorship. In Palade's words, "The circumstances that permitted this development were unusually favorable: we didn't have to worry about research funds (because we were well supported by Herbert Gasser), we had practically complete freedom in selecting our targets, strong competitors who kept us alert, and excellent collaborators who helped us in maintaining our advance."

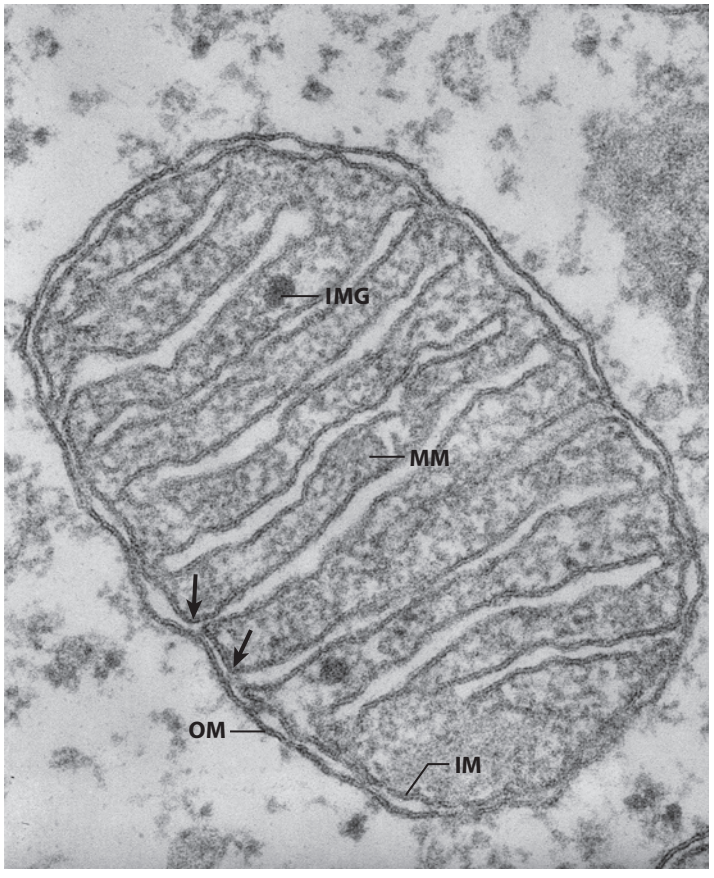

Figure 1

Electron micrograph of a section through a mitochondrion (hepatocyte, rat) showing the cristae, or "cristae mitochondriales," which represent infoldings of the inner mitochondrial membrane (*arrows*) (shown × 100,000). Images from the George E. Palade EM Collection. Abbreviations: IM, inner membrane; IMG, intramitochondrial granule; MM, mitochondrial matrix; OM, outer membrane.

Return to Cell Fractionation: Identification of Microsomes and Studies on Functions of Ribosomes in Protein Synthesis

In 1955 Palade decided to go back to cell fractionation, as it was clearly needed in order to determine the chemical composition and the function of the newly discovered "small particulate component of the cytoplasm" and other structures discovered in the electron microscope. He brought Philip Siekevitz to the Rockefeller to start 18 years of fruitful collaboration, which involved isolation and characterization of different cell organelles through biochemical analysis of subcellular components using electron microcopy to monitor the fractionation. Together, Palade and Siekevitz identified the "microsomes" of Claude (**Figures 2** and **3**) as fragments of the ER (Palade & Siekevitz 1956a,b). Further work led to the isolation of ribosomes either from microsomal membranes (attached ribosomes)

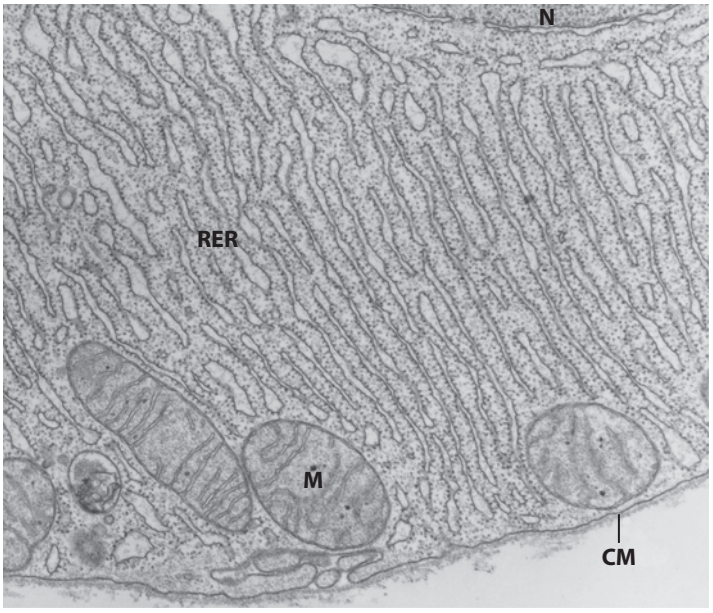

Figure 2

Pancreatic exocrine cell. The basal region of the cell between the nucleus (N) and the plasmalemma (CM) is occupied by numerous cisternae of the rough endoplasmic reticulum (RER) and a few mitochondria (M) (shown × 9,000) (from Palade 1966).

or from microsomal supernatants (free ribosomes) and the demonstration that these organelles are the cytoplasmic sites of protein synthesis (Kirsch et al. 1960). These combined biochemical and morphological studies, mainly on liver and the exocrine pancreas (**Figures 2** and **3**), had closed the loop between the discovery of ribosomes by electron microscopy and characterization of their function in protein synthesis by biochemistry.

Impact of the Work of the Rockefeller Group on the Development of Electron Microscopy and Cell Biology

During this period, not only was the work of the Rockefeller group pivotal in terms of technical development, but it also set high technical and conceptual standards in the field, with emphasis placed on the necessity to link structure and function. The lab was considered the most diversified and advanced in the country for research in biological electron microscopy, and their every discovery was closely followed through presentations at the American Association of Anatomists, the Histochemical Society, the Electron Microscope Society of America (before 1960), and the American Society of Cell Biology (after 1960). The laboratory also functioned as the main training center for biological electron microscopy and was filled with pilgrims at all levels, from distinguished professors and visiting scientists from all over the world, such as Sanford Palay (Harvard), George Pappas (Illinois), Don Fawcett (then at Cornell), Guido Majno (Harvard), Lars Ernster (Karolinska), and later Ewald Weibel (Zurich), to bright young postdoctoral fellows and graduate students (Peter Satir, Lee Peachey, Jack Kirsch, David Luck, David Sabatini, and later Jim Jamieson). All had come to gain proficiency in state-of-the-art methods for electron microscopy and/or cell fractionation in order to pursue diversified biological problems. During this period, Palade and Porter ran into difficulties in publishing their work, particularly in the *Journal of Experimental Medicine*, published by the Rockefeller Press. Palade explained that this was because "the new field and its new proponents were considered too new and untested and the findings too far from the mainstream of current knowledge to warrant publication in the Journal" (G. Palade, personal communication). At the time, neither Porter nor Palade was a tenured professor (they received tenure in 1956), and they lacked the associated status and influence that goes with this step; however, not to be deterred, with the help of Stanley Bennett (then at the University of Washington) and others at Rockefeller they convinced Detlev Bronk, president of the Rockefeller at the time, to start a new journal. Keith Porter's organizational skills were then brought to the fore, and the *Journal of Biochemical and Biophysical Cytology* was born in 1955 and later (in 1962) renamed the *Journal of Cell Biology*. Porter was the first editor, and the editorial board contained many leaders in biological and biophysical electron microscopy of the day, including Palade. It was during this

period that cell biology became a recognized field of research in biological sciences.

Personal Reflections and Experiences during this Period

I began my research career in 1953. After graduating from Berkeley and attending medical school at University of California, San Francisco (UCSF), I decided to work toward a PhD in experimental pathology instead of completing my medical studies. By an extraordinary stroke of luck, it happened that my professor, who was the Chair of Pathology, had just bought a new RCA 3B electron microscope—the first at UCSF—and had no idea how to use it or how to prepare tissues for electron microscopic analysis, so he assigned me the task of "making things work." Like others at the time, we had to set up everything from scratch by taking advantage of what we found in the literature and by consulting with other electron microscopy labs. In this way we gained knowledge of the best preparatory methods of the day. Our initial sections and micrographs were rather crude, but the situation improved dramatically in 1954, when we were fortunate to be able to purchase one of the first Porter-Blum microtomes to be released commercially. Immediately after unpacking it, I sat down and cut the thinnest sections I had ever seen (silver to gold) of contemporary quality and was astounded to see the new world they opened when examined in the electron microscope. My thesis project was to characterize the ultrastructural events that occur during hormone secretion in the anterior pituitary gland using the approach of the experimental endocrinologist (target organ ablation and hormone replacement), a topic in which I had developed an interest during my medical studies. My thesis work produced the first description of granule formation in the Golgi complex and the first description of exocytosis in the anterior pituitary gland (Farquhar 1961, Farquhar & Rinehart 1954, Farquhar & Wellings 1957). At the same time, I also investigated the renal glomerulus in various kidney diseases, which was a main interest of my thesis advisor. And during a year spent at the University of Minnesota, I had the opportunity to examine, with Robert Good and Robert Vernier, the first renal biopsies from patients with kidney disease in the electron microscope (Farquhar et al. 1957a,b). As a graduate student I was also fortunate to be able to attend a meeting of the Electron Microscope Society of America in 1954, where I first met Palade, Porter, Fawcett, and many other pioneers in electron microscopy and was exposed to the standards and discoveries of the day. At that meeting, among others, I heard the first description of the discovery of the "small particulate component of the cytoplasm" (Palade 1953b) and the first description of pinocytic vesicles in the endothelium (Palade 1953c), and I heard Porter speak about the results obtained

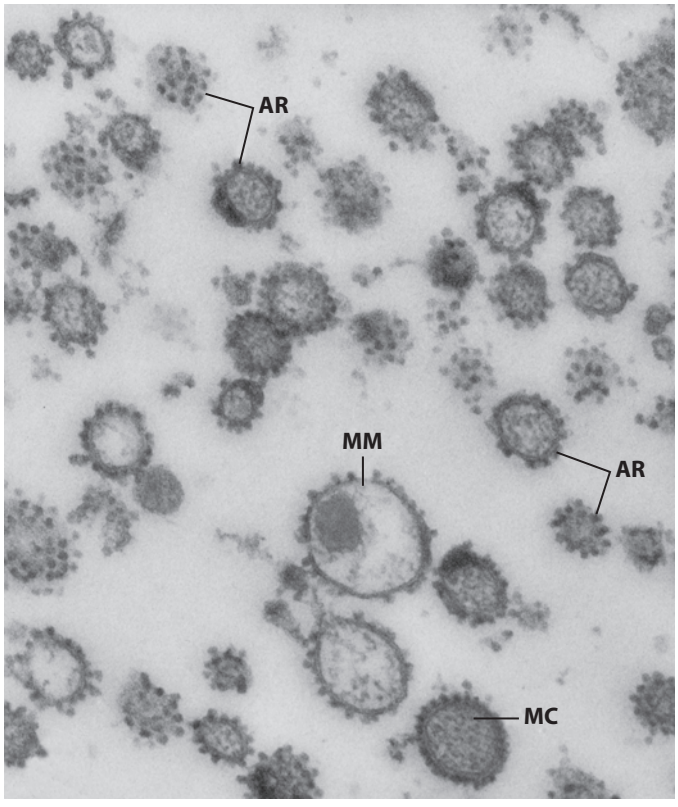

Figure 3

Electron micrograph of a sectioned pellet of pancreatic microsomes (guinea pig) (shown ×60,000; from Palade 1966). Abbreviations: AR, attached ribosomes; MC, microsomal content; MM, microsomal membrane.

with his new Porter-Blum microtome. The air was filled with excitement and electricity, and it is no wonder that I decided—on the spot—that this new field of cell structure and function was right for me.

Work on Glomerular Permeability

It happened that shortly after completing my thesis work I had the opportunity to spend a few years (1958–1961) in New York and—by another stroke of luck—was fortunate to be accepted by Palade as a postdoctoral trainee. For a self-taught graduate student who had worked largely in an empty lab alone and who was the only one with expertise in electron microscopy at UCSF at that time, it was an amazing experience to be translocated into the highly charged, bustling and stimulating atmosphere of the Porter-Palade lab of the period, which was packed to the limit with people at all rungs of the academic ladder from staff to graduate students to important professors. An aura of great excitement prevailed, and everyone was caught up in frenzied activity, with electron microscopes and microtomes booked day and night and throughout the weekends. Upon my arrival, I was told that there were two desks open—one in the dishwashing facility and the other in the hallway. I chose the dishwashing facility and sat beside an important professor from Japan, Eichi Yamada, and back to back with the dishwasher, Marie. The very next day Guido Majno, a professor from Harvard, arrived and was assigned the desk in the hall.

Palade had an ongoing interest in capillary structure and had already initiated a project aimed at using ferritin as a tracer to study capillary permeability, along with a postdoctoral fellow, Steve Wissig. Wissig had succeeded in purifying ferritin, but he had to leave to take a faculty position at UCSF after only one year at Rockefeller and was not able to realize the fruits of his efforts. Based on my experience working on the renal glomerulus, it was agreed that I would continue this project. The very first experiments I did—which involved injecting ferritin into normal and nephrotic rats—were highly successful and yielded important information on glomerular permeability. They demonstrated that in glomerular capillaries the basement membrane is the main diffusion barrier for large molecules, as normally ferritin penetrates the endothelial fenestrae but does not penetrate the glomerular basement membrane (GBM), and in nephrotic animals, which leak protein into the urine, ferritin penetrates the GBM to a much greater extent (Farquhar & Palade 1961, Farquhar et al. 1961). We also showed that the glomerular epithelial cell or podocyte partially recovers the macromolecules lost from the plasma by uptake in small vesicles (Farquhar & Palade 1960) (later named endocytosis), and that the mesangial cells remove filtration residues that accumulate against the GBM (Farquhar & Palade 1962). Later on, with Romain Bruns and Nicolae and Maya Simionescu, Palade used ferritin to study the permeability of other types of capillaries (see below). To this day, ferritin is still used as a tracer to study the permeability of glomerular capillaries.

Discovery of Junctional Complexes

It was during the course of our work on nephrotic rats that we discovered and described the tight junctions and adherens junctions and their organization into junctional complexes. In the nephrotic animal and in humans with the nephrotic syndrome, the glomerular epithelium undergoes a remarkable transformation in that its usual organization into foot processes and filtration slits is replaced by broad swaths of cytoplasm stretching across the outer surface of the GBM. I had discovered this process, referred to as "foot process effacement," earlier in biopsies from human patients with nephrotic syndrome (Farquhar et al. 1957a,b). While carrying out the work with ferritin, I noted that the junctions between the glomerular epithelial cells in the leaky glomeruli of nephrotic rats were fewer and tighter and represented areas where the membranes of two adjoining cells came together and fused, and we dubbed them "tight

junctions." Then I noticed that similar tight junctions were present between the epithelial cells lining the kidney tubules. A survey of epithelia from the endocrine (thyroid), digestive (intestine, stomach, liver), and urinary system (Farquhar & Palade 1963), and later on from frog skin (Farquhar & Palade 1965), resulted in the first description of the distinctive morphologic features of tight junctions and adherens junctions, their organization into characteristic apical junctional complexes (which often include desmosomes), and the demonstration that functionally the tight junction acts as a diffusion barrier or "seal" that prevents passage of proteins along the intercellular spaces. As each set of my findings unfolded, the electron micrographs were shared and admired at daily tea along with those of others.

THE PALADE-SIEKEVITZ LABORATORY AT ROCKEFELLER (1962–1973)

The years 1961–1962 marked a period of transition for the Rockefeller Cytology laboratory (renamed Cell Biology in 1967). Porter and his group joined the Biological Laboratories at Harvard, and the remaining Palade-Siekevitz group moved from the crowded quarters in the basement of Theobald Smith Hall to modern and spacious new quarters in the South laboratories—later named Bronk Hall. By this time, the peak of the golden era of electron microscopy had passed and research was concentrated on a few topics, namely membrane biogenesis, protein secretion, and capillary permeability. During the initial part of this period I spent eight years at UCSF developing my own program. During those years, we focused on studying hormone secretion and discovered crinophagy, the process by which excess secretory granules fuse with and are degraded by lysosomes (Smith & Farquhar 1966); explored the functions of coated vesicles in protein uptake in the epididymis and vas deferens (Friend & Farquhar 1967); and provided the first descriptions of biogenesis of neutrophil granules (Bainton & Farquhar 1966, 1968). In 1969 I returned to Rockefeller on sabbatical as a full professor and rejoined the Palade-Siekevitz group, and the next year (in 1970), Palade and I were married. By this time cell biology had been seeded throughout the world. The Palade and Porter trainees alone had started active groups in cell biology in many universities in the United States (e.g., Harvard, Penn, UCSF) and abroad (Milan, Munich). Yet the Rockefeller cell biology laboratory remained a leading center for training in this new field, and the atmosphere remained highly charged with the excitement of new discoveries. The group was younger and more cohesive, and instead of so many established investigators there were more graduate students and postdocs. Ideas and data were freely exchanged daily during afternoon tea between the faculty (Palade, Siekevitz, Luck, Sabatini, Blobel, Jamieson, Farquhar), the visiting faculty (I. Ohad, E. Weibel, N. Simionescu, M. Simionescu, C. Hopkins), and the younger generation of graduate students and postdocs (including L. Greene, V. Marchesi, J. Meldolesi, S. Shor, S. Silverstein, A. Tartakoff, and later on J. Bergeron, D. Borgese, D. Castle, and N.-H. Chua).

Delineating the Secretory Pathway

Based on his interest in protein synthesis and transport, Palade had initiated with Siekevitz a detailed study on the structure and biochemistry of the pancreatic exocrine cell used as a model for cells synthesizing large quantities of proteins for secretion. During the early years the salient points established by this work were the involvement of attached ribosomes in synthesis of secretory proteins and the vectorial transport of proteins from the attached ribosomes to microsomal ER cavities, in collaboration with D. Sabatini and Y. Tashiro (Sabatini et al. 1966), and the demonstration that secretory granules represent sites of stored pancreatic enzymes (Greene et al. 1963). Because some details of the intracellular transport operations could not be solved by cell fractionation procedures, Palade turned to autoradiography at the electron microscopic level

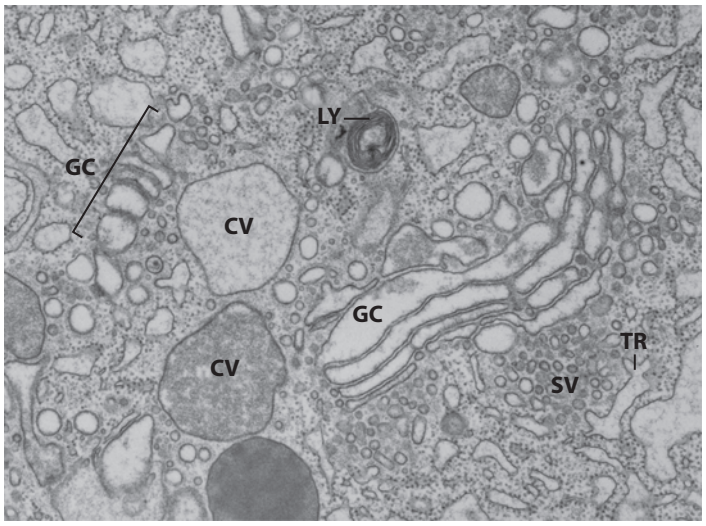

Figure 4

Electron micrograph of the Golgi region in a pancreatic exocrine cell showing the elements of the Golgi complex (shown ×25,000) (from Palade 1966). Abbreviations: CV, condensing vacuoles; GC, Golgi cisternae; SV, small peripheral, ER-Golgi transport vesicles; TR, transitional elements; LY, lysosome.

and, in collaboration with Lucian Caro (Caro & Palade 1964), described the involvement of the Golgi complex in intracellular transport, defined the participation of large Golgi "condensing vacuoles" in the concentration of secretory proteins, and showed that these vacuoles become secretion granules (zymogen granules) by progressive filling and concentration of their content (**Figures 4** and **5**). During the period 1965–1971, in collaboration with Jim Jamieson, Palade used a system of pancreatic tissue slices for pulse-labeling and autoradiography to study the dynamics of intracellular transport of secretory proteins (Jamieson & Palade 1966, 1967a,b). This work brought together all the previous work on the pancreatic exocrine cell and crystallized the now classical view of the secretory pathway, i.e., that transport along the secretory pathway is vectorial—from ribosomes attached to the rough ER, to the Golgi complex, to secretion granules that are discharged by exocytosis at the plasma membrane. It is this topic that was later the focus of Palade's Nobel Lecture (Palade 1975a). The use of the pancreatic acinar cell as a model to study the secretory process was crucial in the success of this work, as it was known that this cell devotes 99% of its protein synthetic activity to producing exportable digestive enzymes. This is an example of one of Palade's secrets of success—namely, his ability to select the optimal experimental system for the cell process under study.

Research on Membrane Biogenesis

Because the discoveries with the electron microscope had revealed that membranes play such an important role in cell organization and cell physiology, Palade initiated a series of studies on membrane biogenesis. In collaboration with Meldolesi and Jamieson (Meldolesi et al. 1971a–c), he isolated the membranes of rough microsomes, Golgi complex, zymogen granules, and the plasma membrane. The comparative biochemistry revealed that membranes of different organelles are quite different in both their protein and lipid composition. Later, with Ehrenrich, Bergeron, and me (Bergeron et al. 1973, Farquhar et al. 1974), he isolated enriched Golgi fractions, and it was established that fractions enriched in *cis*- and *trans*-Golgi elements also differed in their membrane composition: there were minimal overlaps and many enzymatic activities, with each restricted to a particular type of membrane. This specificity of membrane composition implied there was no membrane mixing during transport despite the repeated fusion-fission of the membranes involved. Other work done with G. Dallner (Dallner et al. 1966) and A. Leskes (Leskes et al. 1971a,b) on differentiating hepatocytes showed clearly that during cell differentiation, the ER membrane is assembled in a succession of steps, which Palade called "multistep assembly," and that new components are introduced at many sites in the preexisting membranes. With I. Ohad, K. Hoober, and S. Schor (Ohad et al. 1967a,b; Schor et al. 1970) as well as Nam-Hai Chua (Chua et al. 1973, 1976), work on membrane biosynthesis was extended to thylakoid membranes of the green algae *Chlamydomonas reinhardtii*, which had the advantage that membrane biogenesis

can be synchronized, as membranes are made only in the light. The work on *Chlamydomonas* again supported the idea that membranes are assembled in a succession of steps. The evidence of multistep assembly, growth by expansion of preexisting membranes, and asynchronous turnover provided strong arguments against the often-discussed assumption at the time that membrane assembly involved the polymerization of equivalent subunits.

Discovery of Weibel-Palade Bodies

It was during this period that Palade and Ewald Weibel discovered a rod-shaped cytoplasmic organelle in endothelial cells (**Figures 6** and **7**), later called the Weibel-Palade body (Weibel & Palade 1964). Subsequent studies over the next decades established that these organelles are unique to endothelial cells and thus serve as unambiguous structural markers of endothelial cells in culture. In 1982, Denisa Wagner discovered that they house von Willebrand factor and therefore are clearly related to the blood coagulation system, and the structure of this factor determines their characteristic rod shape. Later on they were also shown to contain the vasoconstrictor endothelin and tissue plasminogen activator as well as P-selectin. Weibel-Palade bodies, which just celebrated their 50th anniversary (Weibel 2012), are now understood to be secretory granules that are released by secretagogues produced by injury or inflammation, which play important roles in endothelial biology by regulating hemostasis, vascular tone, inflammation, and angiogenesis (Wagner & Frenette 2008). Interestingly, this is the only cell organelle that bears Palade's name, even though he discovered others. For a brief time what he had described as "the small particulate component of the cytoplasm" were called "Palade granules" or "Palade's particles," but these were soon replaced with "ribosomes."

MIGRATION TO YALE AND OUTREACH TO MEDICINE

During the late 1960s and early 1970s there were several attempts to lure Palade and his group away from Rockefeller and to start new cell biology departments in different schools of medicine. Palade was attracted by the idea of taking cell biology to medicine, as he was convinced that the future of medicine

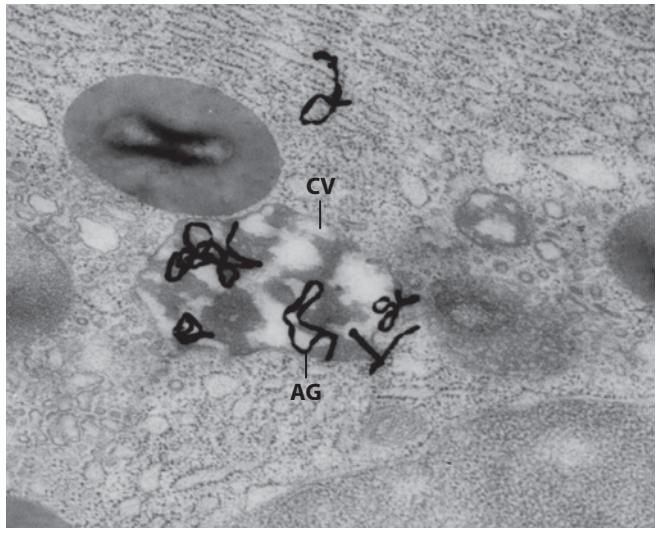

Figure 5

Electron microscopic autoradiograph of the Golgi region in a pancreatic exocrine cell (guinea pig) showing a high concentration of autoradiographic grains (AG) over a condensing vacuole (CV) 40 min after the injection of ^{3}H leucine (shown ×30,000) (from Palade 1966).

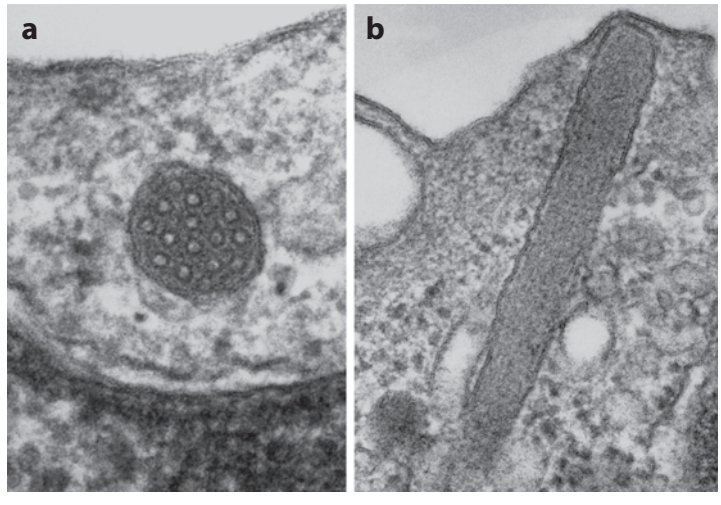

Figure 6

Weibel-Palade bodies in human umbilical vein, showing the unique tubular structure of their content in (*a*) cross section (shown ×180,000) and (*b*) oblique section (shown ×90,000) (from Weibel 2012).

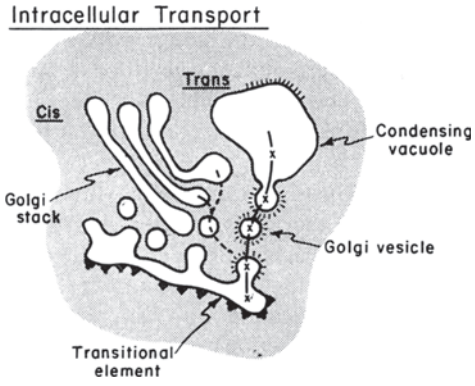

Figure 7

Diagram of intracellular transport; x–x, pathway followed in the pancreatic exocrine cell of the guinea pig; - - -, pathway followed in other glandular cells (from Palade 1975a).

depended on using the information from the new discipline of cell biology to understand the cellular and molecular basis of diseases. In 1972 Lewis Thomas, who was then Dean of the School of Medicine at Yale, raised the resources necessary to bring Palade, together with Jamieson and me, to Yale to start a new section of cell biology. The move was made possible by the generosity of the Commonwealth Foundation directed by Robert Glaser, who had made an unsuccessful attempt earlier to attract Palade to Stanford when he was Dean of the School of Medicine there. Thus in 1973, Palade, Jamieson, and I, and our collaborators, left the cloistered atmosphere represented by the Rockefeller and moved to Yale to start a new adventure. In his own words, "The main reason for the move was my 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" (Palade 1975b). The year 1973 represented a time of major transition for cell biology at the Rockefeller: The three of us with our postdocs and graduate students left for Yale, and David Sabatini moved with his group to become head of Cell Biology at New York University; however, the Rockefeller had been richly seeded in cell biology by the Palade group: Blobel, Siekevitz, David Luck, and Nam-Hai Chua remained at Rockefeller. In addition, Christian de Duve, James Hirsch, and Zanvil Cohn had ongoing, active research programs in cell biology at the Rockefeller.

Organization and Recruitment for the Section of Cell Biology at Yale

We set up the new unit as an autonomous Section of Cell Biology—not yet considered a department—in the style of the Palade-Siekevitz lab at the Rockefeller, where equipment was shared, and although faculty members had independent research programs, their labs and interests were closely intertwined. This was unusual for Yale because at the time it was more common for each professor to function in an isolated kingdom apart from peers. A large part of our energies were devoted to department building and recruitment and to initiating a new graduate program in cell biology. Palade decided to build the department around the common theme of membrane biology and the new field of membrane trafficking. Initially David Castle and Ann Hubbard were recruited as assistant professors, and later on Ari Helenius, Ira Mellman, Peter Novick, and Susan Ferro-Novick were added. These new faculty, along with Palade, Jamieson, and me, made the group collectively one of the strongest in the country with this research focus. Collaborations and interactions were common due to overlapping interests and were strengthened by program project and center grants. A steady stream of postdoctoral fellows, graduate students, and MD/PhD students, as well as MD-fellows and medical students who were required to do a thesis for graduation, joined the active laboratories of the faculty.

Focus on Teaching

At Rockefeller, most teaching was done one on one at the bench, and little emphasis was placed on organized teaching. Palade and Porter had started one of the first comprehensive courses for graduate students at Rockefeller, which Palade directed, and it was there that he

exploited his gift for teaching. The course was highly successful and introduced generations of Rockefeller graduate students to principles of cell structure and function. To carry out our mission at Yale, a major emphasis was placed on further developing an existing course for medical students, started by Russell Barrnett and Tom Lentz, which combined cell biology and histology. I took on the job of course director, and Palade prepared model lectures in which the emphasis was on how the functions of complex organs such as the liver resulted from the integration of the properties of basic tissue types determined by their fundamental building blocks, individual cells. Faculty, students, and postdocs alike were "encouraged" to attend all lectures as part of their training as future teachers, and those of us who did will always remember Palade's hallmark theme from Virchow (1858): "*Omnis cellula e cellula*" (everything begins and ends in the cell). The topics ranged from ribosomes and the structure and function of the liver to the organization of epithelia. Given his breadth of knowledge and gift for integrating pathophysiological and clinical relevance into his teaching (a disappearing skill that reflected Palade's training as a physician), each lecture was a nearly perfect masterpiece with a unique perspective. The faculty followed his example, and the course became the most popular of the basic science courses at Yale. It was attended not only by first-year medical students and graduate students from multiple departments but also by many faculty in both clinical and basic science departments, who were curious and hungry for the integrated information and perspective provided. Our syllabi and lecture notes were also requested and circulated to other faculty in medical schools throughout the United States and even abroad for those who wished to start similar courses. In addition to medical student courses, we also soon developed a vigorous graduate program. Again Palade set the example and provided a model by starting a memorable seminar course in membrane biology that began as a small seminar for 15–20 students and grew into a major lecture course accompanied by a reading seminar.

The Calling for Public Service

Some scientists are content simply to stick to their own careers and follow their imagination and scientific findings wherever they take them. Others have the "public service gene" and feel the calling to devote part of their energy to developing their departments, universities, or professional organizations. Palade had developed a very strong commitment to broader service and derived great satisfaction from such outreach, which began when he was at Rockefeller. Together Porter and Palade initiated and managed what became the *Journal of Cell Biology* and initiated the first formal lecture course at Rockefeller before they were tenured full professors. Later on, after the departure of Porter for Harvard and until the migration of Palade to Yale (1961–1973), the *Journal of Cell Biology* was run out of the Palade-Siekevitz laboratory at Rockefeller by Raymond Griffiths, an MD. Palade personally supervised the flow and handling of manuscripts and devoted considerable attention to making sure that all reviews were rigorous, fair, and above all, constructive. At Rockefeller he served on the faculty council, which he organized as a mechanism to provide feedback and academic input from the Rockefeller faculty to the president of the university. The migration to Yale in itself represented an example of such academic outreach, as bringing cell biology to Yale required considerable effort and greater teaching and administrative responsibilities than was the case at Rockefeller. Palade also served as President of the American Society of Cell Biology and on numerous editorial boards and review committees, and he was the founding editor of the *Annual Review of Cell and Developmental Biology* and served as its editor for 10 years.

The Nobel Prize

Just one year after moving to Yale, Palade was awarded the Nobel Prize in Physiology or Medicine jointly with Albert Claude and Christian de Duve "for their discoveries concerning the structural and functional

organization of the cell." His Nobel Lecture, titled "The Intracellular Aspects of the Process of Protein Synthesis," (Palade 1975a) reveals his breadth and remarkable integrative abilities; it summarizes 20 years of work on the secretory process with biochemical data and state-of-the-art electron micrographs as well as Palade's hand drawings (**Figure 7**), and it is written in the analytical style with historical perspective that is characteristic of his papers as well as his reviews. His papers are refreshing to read because today most scientists do not take the time, or perhaps do not have the broad knowledge, to achieve the breadth and depth of integration and historical perspective that characterized Palade's analysis of a given topic. In his thank-you speech at the Nobel banquet, Palade (1975c) revealed his poetic nature in the following: "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. . . . Cell Biology finally makes possible a century old dream: that of analysis of diseases, at the cellular level—the first step toward their final control."

Although by this time he had received many prestigious prizes, including the Gairdner Special Award, the Louisa Gross Horwitz Prize of Columbia University, and the Lasker Basic Science Award (Palade 1966), and later received the National Medal of Science, this was quite different. The Nobel is considered the highest of all honors that can be awarded to a scientist and definitely represented the beginning of a new phase of his career. Life would never be quite the same again in terms of both the enormous recognition and demands from the scientific public that followed. With the prize also came responsibility and opportunity, and Palade used his new recognition and influence as a bully pulpit to advance basic science in multiple ways, from serving as a reviewer of chairs, graduate programs, and entire departments, to promoting funding by the NIH. For example, he was a member of the Delegation for Basic Biomedical Research organized by Mahlon Hoagland together with a knowledgeable Washington adviser, Brady Matheney. In addition to Palade, the group initially included Max Cowan, Donald Frederickson, Seymour Kety, Arthur Kornberg, Francis Moore, Lewis Thomas, and James Watson. This stellar group was highly successful in increasing funding for NIH in the 1970s and 1980s and spawned other such groups that followed. Palade was also frequently asked to serve as a member of NIH advisory councils (e.g., to the National Institute of General Medical Sciences and the director's Board of Advisors) and to serve on advisory and planning committees to reorganize biological sciences in universities (e.g., University of California, Berkeley) or to provide advice on the research priorities of companies (e.g., DNAX). Based on his breadth of knowledge of cell biology and medicine, his analytical abilities to identify the important unanswered questions of the day, his ability to identify promising new future directions, and the seriousness and dedication with which he took on each assignment, he was highly sought after as an organizer or summarizer of meetings (Palade 1982).

Research at Yale: Unraveling the Structural Basis for Capillary Permeability and the Transport of Macromolecules Across the Endothelium

Although Palade had far less time to devote to research at Yale, especially after receiving the Nobel Prize, even as a busy chair and with all his outside commitments he still succeeded in publishing six to eight papers per year and in maintaining active groups in the fields of membrane biology and capillary permeability. Palade worked intensively and tirelessly during his entire career on trying to unravel the structural basis of capillary permeability. His interest in this topic dated from the 1950s (Palade 1953b, 1960), during the golden age of fine structure, when he discovered that the endothelial cells of muscle capillaries contained a large population of vesicles of ~70 nm

diameter, which he named plasmalemmal vesicles (PVs) (**Figure 8**). He hypothesized that they were involved in transport of macromolecules across the capillary wall and first introduced the idea of "transport in quanta" (Palade 1960). He put this to the test systematically in studies carried out initially at Rockefeller with Romain Bruns (Bruns & Palade 1968a,b; Palade & Bruns 1968), using ferritin as a tracer, and identified the PVs as the structural equivalent of the large pores postulated by capillary physiologists. This work was more fully developed, tested, and greatly extended in a highly fruitful collaboration with Nicolae and Maya Simionescu, which was begun at Rockefeller and continued at Yale and at the Institute of Cell Biology and Pathology in Bucharest. The Institute was the dream of the Simionescus', but Palade's collaborative work with the Simionescus, his devotion to fostering science in his native Romania, and his reputation and prestige were key factors that enabled its creation. It was a miracle that this came about during the Ceausescu era behind the Iron Curtain. Many us who were associated with Palade and the Simionescus at Rockefeller traveled to Bucharest in September, 1979, to participate in an inaugural symposium designed to bring modern science to the young Romanians (**Figure 9**).

The capillary physiologists did not accept the concept of transport by PVs because it did not fit their classical view of transport through aqueous pores, which they assumed to be located at the cell junctions. Thus to further strengthen the evidence for transcytosis in PVs, Palade and the Simionescus utilized tracers of smaller dimensions, including dextrans and glycogen (4.5–30 nm diameter) (Simionescu & Palade 1971), myoglobin (Mr 17,800) (Simionescu et al. 1973), and heme-peptides derived from cytochrome C (2-nm diameter) (Simionescu et al. 1975b). They introduced rapid fixation methods and carried out time-course experiments that allowed the sequential visualization of the probes as soon as 30–60 s after their IV administration. In all these cases the evidence for transport via PVs in continuous endothelium of muscle capillaries was striking (**Figure 10**), and it greatly strengthened the concept that (*a*) transport occurs by transcytosis, and (*b*) the PVs are the structural equivalent of the large pores. No evidence was obtained for transport of any of these tracers through the tight junctions. An important bonus of these experiments was the clear evidence for the existence, in muscle capillaries, of patent transendothelial channels formed by one, two, or more vesicles that open simultaneously on both endothelial cell fronts. They concluded that the transendothelial channels are the most likely candidates for the structural equivalents of the small pores because they are continuous, water-filled passages provided with one or more strictures of 10 nm (Simionescu et al. 1975b). Taken together these experiments provided an enormous body of novel, state-of-the-art evidence that in continuous endothelium, small molecules cross the vascular wall via PVs that can either function as isolated units shuttling across the endothelium or fuse with one another to form patent transendothelial channels.

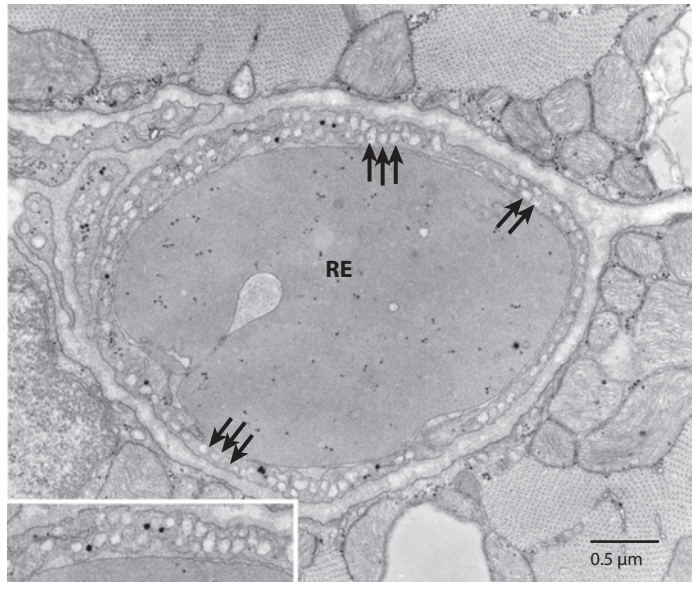

Figure 8

Capillary from rat diaphragm containing a reticulocyte (RE). The endothelium is very thin and filled with numerous plasmalemmal vesicles (*arrows*). Two rows of vesicles are enlarged in the inset (shown ×26,000). From the George E. Palade EM slide Collection, Yale University School of Medicine.

Figure 9

Speakers for symposium celebrating the opening of the Institute of Cellular Biology and Pathology (ICBP) in 1979. Front row (*left to right*): Werner Franke, Maya Simionescu, Gunter Blobel, Marilyn Farquhar, George Palade, Christian de Duve, Nicolae Simionescu, David D. Sabatini. Back rows: symposium attendees.

In addition to muscle capillaries, Palade, along with Francesco Clementi (Clementi & Palade 1969), also extended his studies on capillary permeability to those of the "fenestrated" type found in intestine using probe molecules for the large as well as the small pores (ferritin and horseradish peroxidase). He obtained evidence that both the large and the small pores are in the diaphragms that bridge the endothelial fenestrae. The findings on the large pores were further developed and solidified in work carried out with the Simionescus using exogenous glycogen and dextrans (Simionescu et al. 1972).

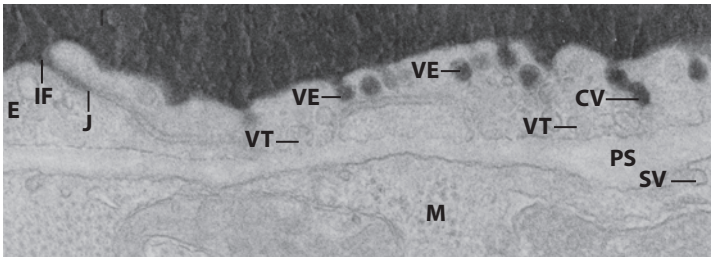

Figure 10

Endothelium from rat diaphragm at 30 s after an IV injection of myoglobin. Myoglobin marks the vesicles (VE) on the luminal front but has not yet reached the tissue front where the vesicles (VT) lack myoglobin. The intercellular spaces beyond the junction (J) appear free of myoglobin (shown ×32,000) (from Simionescu et al. 1973). Abbreviations: CV, chain of fused vesicles; E, endothelium; IF, opening to intercellular space; M, muscle cell; PS, pericapillary extracellular space; SV, sarcolemmal vesicle.

Palade was also interested in characterizing and analyzing the fine structure and the functional properties of different regions of the microvasculature, i.e., arteries, veins, capillaries, and venules, under normal and pathological circumstances. Early on, in work carried out with Guido Majno (Majno & Palade 1961, Majno et al. 1961) at Rockefeller based on the topical application of histamine and serotonin, he established that the increased permeability of the vascular bed in experimental inflammation is owing to focal separation of the endothelial cells from one another. They further established for the first time that such separations are restricted to small venules and venous ends of capillaries. Later on he and the Simionescus characterized the detailed organization of the junctions in different segments of the microvasculature (Simionescu et al. 1975a) and

established the permeability properties of the different regions of the vasculature (Simionescu et al. 1976). Using charge probes and lectins they also demonstrated the existence of differentiated microdomains of different chemical composition on the endothelial cell membrane that were assumed to represent areas with selective permeability properties (Simionescu et al. 1981a,b; Simionescu et al. 1982).

Membrane Biogenesis and Membrane Trafficking

During his time at Yale, Palade continued to characterize the subcompartments of the secretory pathway and to identify the commonalities in membrane trafficking as well as the unique features of protein traffic in distinct cell types. He and K. Howell (Howell et al. 1978, Howell & Palade 1982) developed sophisticated fractionation techniques to isolate and characterize distinct subcompartments of hepatic Golgi fractions and developed procedures for separating Golgi membrane proteins from content proteins and for assessing contaminants from the cytosol. These separation protocols form the foundation of now generally utilized techniques for classifying the different types of protein association with membranes. With David Castle (Castle et al. 1975, Castle & Palade 1978), he expanded the pancreatic secretion paradigm by showing analogous regulatory mechanisms in cells of the parotid gland.

Palade also provided insight into specialized secretory pathways and, with Elizabeth Sztul (Sztul et al. 1983, 1985a,b), identified a novel transcellular pathway utilized by the polymeric IgA receptor (pIgA-R) that traffics from the Golgi complex first to the sinusoidal plasma membrane of hepatocytes and then transcytoses to the bile canalicular plasma membrane and worked out the details of pIgA-R biogenesis that regulate the pIgA-R itinerary. The mechanism of polarized delivery of membrane proteins to the apical and basolateral domains of MDCK cells was investigated with Michael Caplan and Jamieson (Caplan et al. 1987, 1990). These early studies set the foundation

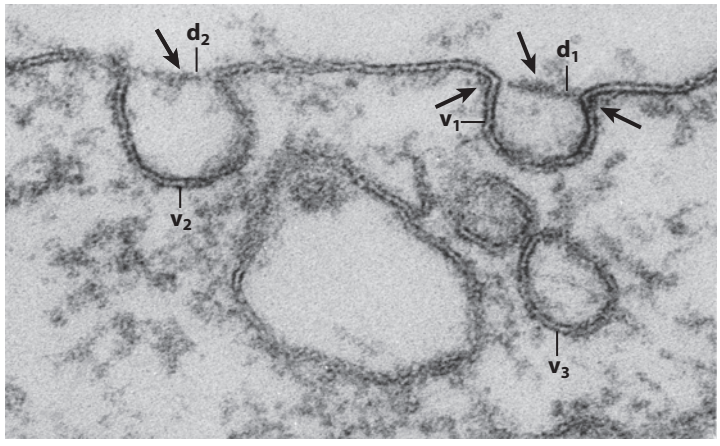

Figure 11

Endothelium from a heart capillary showing plasmalemmal vesicles (v_1, v_2, v_3) with their stomatal diaphragms (*arrows*; d_1, d_2) (from the George E. Palade EM Collection).

for subsequent analyses of cell-dependent trafficking pathways in other cell types.

During this period, Palade also expanded his interest in membrane biogenesis to that of red blood cell membrane proteins. He and Andreas Sarris (Sarris & Palade 1979, 1982a,b) were the first to detect O-acetylated sialyl residues on erythrocyte membrane proteins, and he, Jeff Ulmer, and Elizabeth Dolci (Ulmer et al. 1989, Ulmer & Palade 1989) described alterations in the glycosylation of glycophorins in erythroleukemia cells and showed that they lack N-linked oligosaccharide chains and are mostly O-linked. Palade also continued his work on membrane biogenesis in chloroplasts, and with L. Bourguinon (Bourguignon & Palade 1976) studied how cells regulate the synthesis of chloroplast thylakoid membranes during the cell cycle.

Also while at Yale, Palade pioneered an immunoisolation approach as a means of selectively purifying elements such as clathrin-coated vesicles and transcytotic vesicles that cannot be readily separated by conventional fractionation procedures based on size or density. These studies represent some of the earliest attempts to use immunoisolation to recover minority cellular elements for biochemical analysis and for morphologic survey

of the fractions by electron microscopy (Howell et al. 1988, Ito & Palade 1978, Merisko et al. 1982). These groundbreaking analyses led to the development of immunoisolation protocols that now represent one of the most routinely used approaches in cell biology. In addition, immunoisolation procedures led to the subsequent development of in vitro reconstituted systems that allowed the dissection of key events during membrane trafficking. Thus throughout his 17 years at Yale, Palade generated key findings on how membrane and secretory proteins are processed and transported as well as how vesicular trafficking is controlled. By this time, research in membrane trafficking had become increasingly popular, with many molecular biologists, biochemists, and geneticists entering the field.

Palade's main lasting scientific legacy is the establishment of the framework for the secretory pathway that was the basis of all the subsequent studies aimed at elucidating the myriad of molecular events that regulate membrane trafficking through the pathway. His uncanny ability to deduce the implications of traffic progression, to point to important unanswered questions, and to identify promising avenues for future investigation meant that he was highly sought after, for example, to chair sessions at Gordon conferences and to provide perspectives and summaries for meetings and conferences (Palade 1982) concerned with the general problems in the field, especially with how membrane and secretory proteins are processed and transported and how vesicular trafficking is controlled. Never were his integrative and analytical capabilities more evident when, later on (in 1995), at the age of 82, he summarized an information-packed, three-day Cold Spring Harbor meeting with highlights on how the information presented at the meeting had advanced our understanding of the membrane-trafficking field at the time (Palade 1995).

Early Retirement

After 12 years at Yale and building what was considered one of the most successful cell biology groups in the country, Palade reached the age of 70 and was required by Yale rules to step down as Chair of the Section of Cell Biology. The section subsequently was considered mature enough—in fact it was hypermature—to be awarded departmental status, Jamieson assumed the Chair for the next nine years, and the department continued to prosper. However, Palade was full of energy and quite restless and seeking new challenges. Robert Berliner, who was then Dean of the School of Medicine at Yale, took advantage of Palade's unique capabilities as a visionary and arbitrator and invited him to become an advisor to the Dean—a position Palade continued under Berliner's successor, Leon Rosenberg. As Dr. Rosenberg succinctly put it, "no one who attended the Friday morning meetings of the Dean's staff was more carefully heard and listened to than George—not because he was a Nobelist, but because of his vision, clarity, determination, and constructiveness" (L. Rosenberg, personal communication). Palade was convinced that the basic sciences in the medical school at Yale could not grow without building new and modern research facilities. No new research buildings had been built in the medical school for more than 30 years, and Palade was determined to do something about it. Palade initiated the project by organizing a planning committee composed mainly of department chairs whose members included Sam Their, Leon Rosenberg, and Alan Sartorelli. The committee subsequently succeeded in convincing Bart Giamatti, President of Yale, to launch the first fund drive on behalf of the medical school in the history of Yale University. Palade then went on to get the blessing of the Yale Corporation, especially Maxine Singer, the main scientist on the board. As a result, a funding office was opened in the medical school, and a fund drive was launched. Palade had a long-standing, close relationship with Max Cowan, the Scientific Director of the Howard Hughes Medical Research Institute (HHMI) at the time, and they agreed to provide funds toward building a new basic research building and funds for HHMI Investigators at Yale. With a gift from Herbert

Boyer and help from HHMI, ground was broken in 1989 for the Boyer Center for Cellular and Molecular Medicine; the building was completed and the center opened in 1991 with Vincent Marchesi (by coincidence a former postdoctoral fellow with Palade at Rockefeller) as its first director. However, Palade did not remain at Yale long enough to see the building completed and to realize the fruits of his efforts.

GO WEST, YOUNG MAN: A NEW BEGINNING AT UNIVERSITY OF CALIFORNIA, SAN DIEGO

In 1989 Gerard Burrow, who was Vice Chancellor and Dean of the School of Medicine at the University of California, San Diego (UCSD), came to Yale for alumni day, was impressed with the development and construction that was going on, and invited George and me to pay a visit to UCSD. He hoped to recruit Palade as Dean of Science and me as chair of a new department of Cellular and Molecular Medicine. The School of Medicine at UCSD had been set up originally in the 1960s without basic science departments, and the basic sciences (genetics, cell physiology, molecular biology, cell biology, and biochemistry) were taught to first-year medical students by faculty in the Departments of Biology and Chemistry according to what was called the Bonner Plan, and many faculty positions belonging to the School of Medicine resided in those departments for 25 years. At the end of the 25-year contract, the medical school, under Dean Robert Petersdorf, had arranged to retrieve the faculty positions and to use them to build basic sciences in the School of Medicine. A committee chaired by Dan Steinberg had recommended that the first six full-time positions (FTEs, in UC terms) be used to start a new basic science department. With the departure of Dean Petersdorf, Gerard Burrow became Dean and, convinced that this represented a crucial juncture and a unique opportunity for the future of the medical school, decided to recruit a Dean of Science who could assist in planning for the development of basic sciences and in exercising quality control over the filling of the new positions and the development of the new department.

Beyond Retirement Years—The Decision to Begin Again

At the time of the UCSD proposal, Palade had just signed a contract with Harvard Press to write the history of cell biology. However, he preferred new challenges and embarking on new adventures instead of writing history, especially history in which he was a central figure. He and I were both highly attracted by the opportunity to direct the development of basic sciences and to recruit gifted scientists to the medical school at UCSD. This young institution—only 30 years old at that time—already had a strong research heritage in the clinical departments and a prestigious biology department, and it recently had established its first basic science department, the Department of Pharmacology (previously a division of the Department of Medicine), which was destined to become the top pharmacology department in the country. Moreover, La Jolla ("the jewel") collectively already had a rich biomedical science community that included not only UCSD but also the Salk Institute, the Scripps Research Institute, and the Burnham Institute, where Palade and I had many scientific friends and colleagues. It appeared that the environment—both physical and scientific—was ideal for recruitment and for building basic biomedical sciences. Thus it came about that in 1990, at 77 years old, when George was well past the normal retirement age, we moved to UCSD, and he started a new phase of his career as Dean of Science in the School of Medicine. He dedicated the next ten years to this mission while serving under three successive deans/vice chancellors (Gerard Burrow, John Alksne, Ed Holmes).

Initial Challenges and Opportunities

Palade's experience in institution building and his gifts for diplomacy and persuasion, as well as his reputation as a visionary, equipped him well for the job at hand. The first six months after

his arrival at UCSD turned out to be crucial, as there were several ongoing recruitments in progress that Palade was able to facilitate. In particular, attempts were being made to recruit Roger Tsien. Palade stepped in immediately after his arrival and played a crucial role in finalizing the recruitment. Also, the possibility of moving a branch of the Ludwig Institute of Cancer Research, directed by Web Cavenee, to UCSD was being explored. According to Cavenee, he had received permission from the Ludwig administration to move his branch from Montreal to a medical school in the United States. Christian de Duve (a close friend and colleague of Palade who had shared the Nobel Prize with him) was a member of the Ludwig Board of Scientific Advisors and had suggested to Cavenee that his branch should seek to gain strength in cell biology. Cavenee was trying to decide where to relocate. He was attracted by the entrepreneurial, open, and interactive environment at UCSD but considered it to be a young and untested institution and thus a risky environment to develop the new institute. At the crucial time when the decision of where to relocate was under consideration, Cavenee was informed that Palade had accepted to be Dean of Science, and this provided the crucial factor in his decision to move his Ludwig branch to UCSD because, "I knew that with Palade in charge of developing the basic sciences at UCSD, cell biology would be strong and excellent recruitments would be made." As Dean of Science, Palade was also in charge of strengthening the graduate programs in the medical school, and he applied for and obtained funds from the Markey Charitable Foundation for graduate student fellowships in biology and chemistry on the campus and in neurosciences and the biomedical sciences at the School of Medicine. The goal of these fellowships was to attract bright young graduate students who otherwise might not consider coming to UCSD. This program, which was highly successful, continued over eight years and was phased out only when the Markey Foundation itself was phased out and stopped giving grants.

Recruitment for the New Division of Cellular and Molecular Medicine

A main item on our agenda for our recruitment to UCSD was to utilize the positions available to establish an autonomous Division of Cellular and Molecular Medicine that eventually would become the second basic science department in the medical school. To accomplish this, Palade appointed a blue-ribbon search committee composed of leading faculty from UCSD (Jon Singer, Palmer Taylor, Ted Friedman, Susan Taylor, Roger Tsien, Steve Wasserman, Rusty Gage, and me). With the help of this committee and six national searches (1990–1994), we succeeded in recruiting two beginning investigators, C. Glass and X-D. Fu, and three established intermediate career investigators—Scott Emr, Larry Goldstein, and Jamey Marth—from prestigious institutions to start the new department with the author as founding chair. In addition to considerable resources provided by both Dean and Vice Chancellor Burrow and Chancellor Richard Atkinson, a key factor in our successful recruitment of established investigators was the availability of three positions for HHMI investigators that Palade had again negotiated with Max Cowan. The approach used in these recruitments was much broader than for recruitment at Yale. The idea was to bring to UCSD those working in promising and important areas of cell biology, which included not only membrane trafficking (Emr), but also cell motility (Goldstein), glycobiology and mouse genetics (Marth), gene transcription (Glass), and RNA processing (Fu). Several local cell biologists—James Feramisco, Ajit Varki, and Gordon Gill—also received joint appointments in the new Division, and later on, Jeff Esko was recruited to the division. In addition, W. Cavenee, with Palade's help, recruited Don Cleveland and Richard Kolodner, who received joint appointments in the Division. According to Cavenee, Palade was key in their recruitment, as he gave "stature and substance to UCSD, which are important factors to senior people looking to relocate." After eight years,

the Division was finally made a Department, and it has grown and thrived ever since. It now has a faculty of more than 30 and is chaired by Don Cleveland. The wisdom of these choices became evident as each of these recruits were or became leading figures in their fields, and in recent years several have opened up new fields in which they have become leaders, e.g., stem cell research (Goldstein) and epigenetics (Glass and Fu). Several (Emr, Marth) subsequently have left UCSD for other opportunities.

Other Contributions and Palade's Overall Impact on Basic Sciences at University of California, San Diego

While at UCSD, Palade made a perpetual effort to reach out to campus departments and surrounding institutions to bring people together for cooperative projects and to engage in future planning. Those contacted to give their view of the overall impact of Palade on basic sciences at UCSD universally agreed that one of Palade's great strengths was his foresight in seeing that there should be pockets of scientific strength in the many basic science disciplines, regardless of the organizational unit they represented, and in setting high standards for recruitment by insisting on bringing to UCSD only individuals of great stature and promise. As he had done at Yale, he instilled cellular and molecular approaches as the bridging discipline in the basic sciences. As a result, departments or units at UCSD developed wider perspectives, enabling the crossing of boundaries between disciplines. He established the Faculty of Basic Biological Scientists, which brought together a diverse faculty group to assure cross-disciplinary representation with the goal to plan future development of the basic sciences; they discussed topics such as the teaching of basic sciences, identification of fields for future development in the School of Medicine, and the best use of resources such as open FTEs. This group met regularly over a period of 10 years, first under Palade and later, upon his retirement, under G. Gill. During those sessions, immunology and genetics were identified as fields that were high priority for development and expansion at UCSD. Palade dreamed of developing these fields successfully, as he had done for cell biology. These efforts were successful in that they resulted in the recruitment of several promising young investigators in genetics—Tony Wynshaw-Boris (who subsequently moved to UCSF) and Bruce Hamilton, who currently heads the graduate program in genetics. It remained for the present Dean and Vice Chancellor, David Brenner, to provide the required resources to build the strong Genetics and Genomics Program at UCSD that Palade had envisioned.

Research Continues at University of California, San Diego

Remarkably, even in the face of heavy administrative demands posed by his position as Dean of Science, Palade maintained an active laboratory with research focused primarily on the exchange of molecules across cellular barriers. Most of his research was centered on vesicular trafficking in hepatocytes and mechanisms of vascular permeability in capillaries in normal states as well as during angiogenesis and inflammation. Palade's dream before he retired was to gain evidence that would convince capillary physiologists that PVs and transendothelial channels carry out important functions in capillary permeability. Thus he continued to devise new approaches and to study their importance for vascular function in health and disease. With Dan and Sanda Predescu he demonstrated the role of PVs in transport of macromolecular cargo, mainly small proteins (~2–20 Å), across the continuous endothelium of muscle and heart capillaries to further establish the location of the small and large pores of the physiologists (Predescu et al. 1997). A highlight was the demonstration that the universal membrane-fusion machinery—SNARES and NSF—is required for albumin transport across the endothelium, which greatly strengthened the case for vesicular transport by transcytosis across the endothelium (Predescu et al. 1994, 2001).

To gain insight into the precise function(s) of endothelial PVs, one of the major efforts in the Palade laboratory was to isolate PVs and to characterize their components. This was a distinct challenge that called upon Palade's wide experience in cell fractionation and immunoisolation. The first step, worked out in collaboration with Bruce Jacobson and Jan Schnitzer (Jacobson et al. 1992), was to isolate plasma membrane patches in a quasi-pure form using cationized silica nanoparticles. This preparation was the starting material for the later immunoisolation, with Radu Stan and others, of PVs using anti-caveolin 1 antibodies (Stan et al. 1997). Use of the latter was based on findings by others that PVs contain caveolin and correspond to specialized caveolae. The results of these efforts demonstrated distinct differences between PV and other membrane components in the fractions and led to the discovery of the PV1 protein, which Stan purified and cloned (Stan et al. 1997). PV1 was the first component of the stomatal diaphragms (**Figure 11**) of the caveolae (PVs), fenestrae and transendothelial channels to be identified (Stan et al. 1999a,b).

Palade also extended his inquiry on the functional role of PVs and showed they are involved in (*a*) the internalization of thrombin and thrombin receptors (Horvat & Palade 1993), (*b*) platelet-activating factor-induced hyperpermeability in inflammation (Predescu et al. 1996), and (*c*) permeability in vessels undergoing angiogenesis after stimulation with vascular endothelial growth factor (Roberts & Palade 1997).

What is surprising is that, in spite of the depth and breadth of the evidence generated largely by Palade and his numerous collaborators over 50 years, to this day transcytosis and the derived endothelial channels are not accepted by capillary physiologists as major players in endothelial permeability. To this day, they still believe that the large pores are located in the cell junctions, in spite of the fact that there is no direct evidence that such is the case in either the endothelium or in the epithelium. They now acknowledge the existence of the transcytotic pathway but do not believe that PVs and transcytosis play an important role in capillary permeability (Levick & Michel 2010, Michel & Curry 1999, Rippe et al. 2002).

Time for Recharging

In spite of the perpetual academic pressures, Palade and I made sure to make time for recreation and recharging. George read widely and particularly enjoyed history. He greatly appreciated all the fine arts—especially paintings, music, and poetry. He was interested in the Impressionists, and he had an entire bookcase full of art books and a large collection of records and CDs, which we enjoyed regularly. In New York we took full advantage of the museums, opera, theater, and fine cuisine; in New Haven we took advantage of the Yale Repertory and Long Wharf theaters, where we shared season tickets with N. and M. Simionescu; and in San Diego we enjoyed the opera and UCSD theater. We had a policy that when traveling to attend scientific meetings we take some time to enjoy the local cultural offerings. "To restore the soul," we never failed to take in the art museums when traveling—e.g., in Chicago, Washington, San Francisco, Philadelphia, Paris, and Madrid. Particularly memorable were trips to Greece, which included Athens and Olympia (among other places), and our visits to Venice and then to Milan, Ravenna, and Florence, shared with Dee and Cedric Bainton, places where art and history are irrevocably intertwined. George knew more history than most of the guides at the historical landmarks we visited and was impatient with their abbreviated and sometimes inaccurate accounts of historical events.

In addition to these cultural experiences, time was also made for the outdoors and physical activity. We shared a great love and appreciation of natural beauty—especially of the mountains and the beach. In San Diego we took long walks on the Del Mar Beach. In Connecticut we took long hikes in the woods, and George enjoyed the arduous task of cutting

down dead trees on our property. The greatest lift came each summer during our annual escape to Aspen, Colorado. George had grown up hiking in the backcountry of the Carpathian Mountains in Romania, and I had grown up at the foot of the Sierra Nevada and as a teenager was introduced by my father to hiking and horseback riding in the High Sierras. Aspen had and still has it all—unmatched natural beauty, great music with its annual music festival, and many academic connections. We became addicted to Aspen after being invited there to give talks at the Given Institute, established by Donald King in the 1970s. The state-of-the-art conferences he organized from the 1960s through the 1980s brought many scientists to town for the same purposes. After the conferences were over we stayed on to enjoy the music, breathtaking scenery, and high cuisine and spent many hours hiking, where we were joined often by our children, family, and friends, including many scientists such as the Kings, Dee Bainton, Lubert and Andrea Stryer, and Sam and Joan Silverstein. At the summit of each hike George rewarded those who hiked with us with chocolate treats. After three to four weeks of music, strenuous hiking above 9,000 feet, and warm friendship mixed with a little science, we were in very good physical condition, had shed our stress, and came back replenished and ready to start the new academic year.

Retirement

George retired as Dean of Science at the end of 2000, but, at the request of the Dean and Vice Chancellor, Ed Holmes, he continued to serve on the committee of advisors to Jack Dixon, Palade's successor as Dean of Science. "Retirement" meant that he continued to come every day to the university, to serve on the Advisory Committee, and to interact on a frequent basis with his research group. He continued these activities until 2002, when he was past 90, and finally closed his lab and capillary research in 2002, when the "ravages of time" and Parkinson's disease had taken their toll. Throughout this work Palade had been continuously funded by the NIH, and in fact he received a MERIT award from NHLBI when he was 85 and maintained that grant until he was over 90.

In 2004, Dean Holmes made the decision to name the building in which Palade had carried out his research the George Palade Laboratories of Cellular and Molecular Medicine, and a few years later he established the George Palade Chair in Cell and Molecular Medicine, of which the first holder is Peter Novick. He and his wife Susan Ferro-Novick had been recruited to UCSD by the Department of Cellular and Molecular Medicine.

THE PEOPLE LEGACY

In addition to the discoveries, one of the most lasting and rewarding legacies of a scientist are the individuals—the graduate students, postdoctoral fellows, and visiting scientists—who have spent time in their laboratories. Palade left behind a rich scientific lineage of nearly 80 collaborators with whom he published more than 200 papers over his approximately 50-year career. His first-generation collaborators went on to be leaders in the field in the United States and abroad and in turn spawned second-, third-, and fourth-generation cell biologists who populate departments around the world. In addition to the people he trained directly, he provided advice, guidance, and scientific direction to countless others. His door was always open equally to everyone from Yale faculty or UCSD undergraduates to visiting Romanian students who wanted to meet their national idol. In short he listened to and advised everyone who sought his counsel. In addition, he reached out to mentor faculty and students alike. He maintained a high level of interest in every new recruit, was excited to hear about the latest research progress, and often summoned them to his office to hear about their new results. This was done in part as a form of mentorship and in part to obtain his weekly if not daily "fix" of new discoveries, to which he had become addicted in the early years of cell biology.

In 1998, UCSD sponsored a symposium in his honor that was attended by many admiring colleagues and dozens of his devoted former postdocs and graduate students. Some had come from as far as Italy, Romania, and Norway for the occasion. They came to show their respect and affection as well as to show their devotion and appreciation for his strong qualities as a mentor, a role that he took very seriously. Palade was proud of and grateful to those he trained. At the end of the symposium—the last time that Palade appeared on the speaker's podium—he thanked the speakers, the attendees, and his collaborators and noted that the names of his collaborators for him read like the "verses of a poem."

CONCLUDING REMARKS

George Palade was truly "A Man for All Seasons." He had broad interests and knowledge of science, the arts, and history. He died on October 7, 2008, at the age of 95 after a very full and productive life. By coincidence it was the very same day that it was announced that Roger Tsien had been awarded the Nobel Prize in Chemistry for 2008, thus symbolizing the continuity of science and the passing of the torch to the next generation. By another coincidence, Dr. Tsien's laboratory is located in the building dedicated to George Palade, who had been influential in recruiting Tsien to UCSD.

Palade believed that the most important thing in life is to "leave something behind for future generations," and indeed he did. To begin with, he is considered by many to be the father of modern cell biology and leaves behind an unparalleled legacy of discoveries. He also spawned generations of scientific offspring who carry on his scientific legacy, and he made crucial contributions to the development of basic sciences in two major universities. At the same time he remained a consummate gentleman who was sensitive and gracious. All these accomplishments and qualities made him, in the words of David Sabatini, "one of the most admired and beloved figures" of our time.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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