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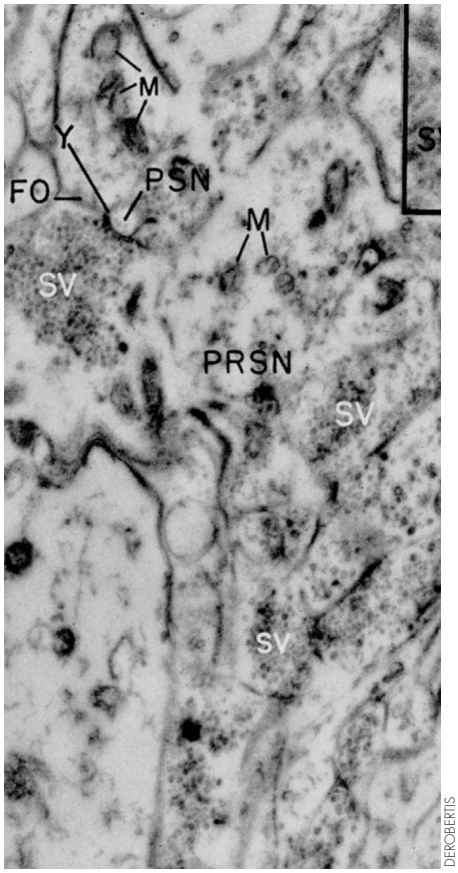


DE ROBERTIS

Synaptic vesicles (SV) near the synapse (Y) of the earthworm.

The discovery of synaptic vesicles

When the *Journal of Cell Biology* was born, in 1955, electron microscopy (EM) was a new but booming source of biological information. As George Palade stated, "the then dormant field of biological morphology" was now undergoing "a period of intense activity, reminiscent of a gold rush . . . only filaments, membranes, and particles have taken the place of more conventional nuggets."

The inadequate reproduction of EM images in existing journals was one of the driving forces for founding the Journal, which until 1962 was called the *Journal of Biophysical and Biochemical Cytology*. Many of the best papers in those first years came from just looking—and having the ability to interpret what all those fuzzy blotches might mean.

A prime example came in the first issue (De Robertis and Bennett, 1955). The synapse had been named in 1897, and by the early 1900s Ramón y Cajal had proposed his neuron doctrine, which predicted that pre- and post-synaptic structures would be constructed from distinct cells that did not show cytoplasmic continuity with each other. Early EMs of synapses in 1953 had largely confirmed this prediction, but it was not until a pair of papers from Palade and Palay (1954) and De Robertis and Bennett (1955) that the messengers of the synapse—synaptic vesicles—were first recognized.

De Robertis and Bennett felt these vesicles "to be of interest and worthy of further study" but cautioned that "no general conclusions [were] warranted." They did, however, make the connection between what they saw and the particulate or granular fractions that in other papers had been found to contain acetylcholine and catecholamines. In a paper the following year, Palay (1956) was even more explicit in proposing that the vesicles visible by EM were the structural source of the miniature, spontaneous pulses reported in a series of papers in 1954. Thus the hypothesis of quantal transmitter release now had a structural correlate. JCB

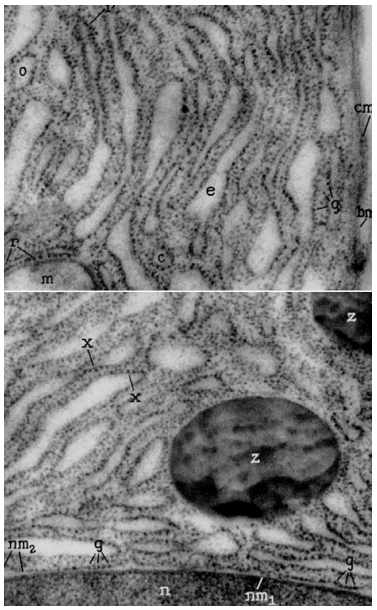
De Robertis, E.D.P., and H.S. Bennett. 1955. *J. Biophys. Biochem. Cytol.* 1:47–58.
Palade, G.E., and S.L. Palay. 1954. *Anat. Rec.* 118:335.
Palay, S.L. 1956. *J. Biophys. Biochem. Cytol.* 2(Suppl):93–202.

Ribosomes, or the particles of Palade

Early electron microscopy (EM) was troubled by, as George Palade put it, "the perennial and arduous question of artifact versus reality." Stains and fixatives could precipitate—Keith Porter referred to this as "the coagulating action of the fixative"—and produce structures that were not present in the original sample.

But when Palade noted a particulate component of the cytoplasm, he confirmed its presence using two different fixatives, and described its particular abundance in embryonic, rapidly proliferating, and glandular cells (Palade, 1955). Thus were born the particles of Palade, later known as ribosomes.

Palade saw that the particles were both on the endoplasmic reticulum (ER) and free in the cytoplasm. Although the ER was identified in 1945 (Porter et al., 1945), by 1955 the terms ER, ergastoplasm, and basophilic cytoplasm were still used almost interchangeably—the last in reference to the staining of RNA-rich areas with basic dyes. Palade realized that not all of the ER had bound ribosomes, and thus the basophilic region referred only to what we would now term the rough ER.



PALADE

Ribosomes, or particles of Palade, in rat pancreas.

This distinction between rough and smooth ER was made even more explicit by Palay and Palade (1955), who found that the so-called Nissl bodies in neurons were none other than clumps of rough ER, which were distinct but connected to sections of "a granular reticulum" or smooth ER. As Palade predicted, the correlation between rough ER and protein synthesis came with later correlative studies using both EM and biochemistry. JCB

Palade, G.F. 1955. *J. Biophys. Biochem. Cytol.* 1:59–68.
Palay, S.L., and G.F. Palade. 1955. *J. Biophys. Biochem. Cytol.* 1:69–88.
Porter, K.R., et al. 1945. *J. Exp. Med.* 81:233–246.

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A new take on the old

This new section is our way of celebrating 50 years of magnificent cell biology in the pages of the *Journal of Cell Biology*. It is, to a first approximation, chronological, but by necessity far from exhaustive. We consciously set out to sketch some high points in the history of the Journal, but not to cover the entirety of cell biology. Papers from other journals are, however, always cited when appropriate.

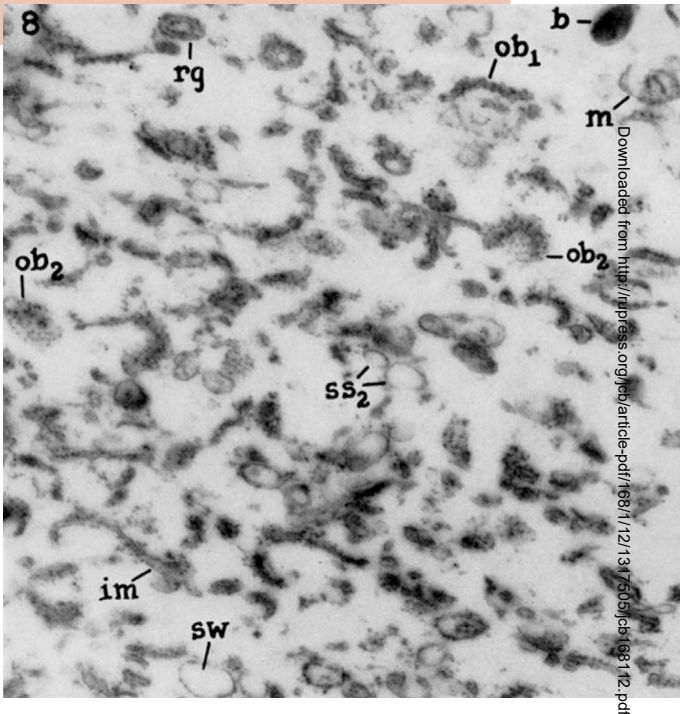
The selection of articles to be covered will always be a subjective process. We tried to improve these judgements by using multiple sources of information: older review articles, citation frequencies and, most importantly, the recommendations of past and present *JCB* editorial board members. Sincere thanks to all those who provided suggestions and helped with context and first-hand accounts of research—research that happened many years ago but that provides many salient lessons for cell biologists working today. Happy reading!

Microsomes are the in vitro ER

The abundance of electron microscope (EM) images in the 1940s and 1950s brought a new problem: nomenclature. What to call all those black smudges? As recalled by Palade (1956), "it appears that, at that time, our group was not yet engaged in large scale production of new cytological terms with a heavy Latin flavor, and was still proceeding with cautious restraint in matters of nomenclature." But there were plenty to take Palade's place.

Perhaps the first connection between two parts of this nomenclature came with a paper by Palade and Siekevitz (1956a). They united the fields of microscopy and fractionation to conclude that Albert Claude's biochemical fraction called microsomes (Claude, 1943) were none other than the in vitro version of the endoplasmic reticulum (ER)—a cytological feature first noted by Keith Porter (Porter, 1953).

Claude had stumbled upon microsomes when he was hunting for Rous sarcoma virus. His RNA-containing fraction was a promising place to find an RNA virus, but unfortunately an identical RNA-containing fraction could be isolated from uninfected cells. Numerous investigators later suggested that microsome fractions were linked to protein synthesis, as they were the first fractions to incorporate radioactive amino acids.



PALADE

Microsomes (here) and ER look similar, and both have ribosomes (see dots near "ob2").

Now, the problem was to find the in vivo correlate of microsomes. Although microsomes from rat liver cells were more fragmented than the original ER, the general structure of the membranous compartment stayed consistent throughout the fractionation. More tellingly, bound "dense particles" (now known as ribosomes) were a characteristic mark of both the in vivo and in vitro structures. The microsomes "could only have come from a fragmentation of the ER," says Siekevitz. "It was the only thing in the cell that they resembled." Detergent treatment then showed that the ribosomes were the RNA-rich components of the ER.

These findings were reproduced in pancreatic cells by Palade and Siekevitz (1956b), who made special note of "the frequent association of the small particles in chains and relatively large, more or less orderly organized masses." At least some of these patterns, and the "parallel double rows, loops, spirals, circles, and rosettes" noted in the original description of ribosomes by Palade (1955) were probably polysomes—a structure whose existence was not fully proven for another 6 years (Warner et al., 1962). During that period Palade had continued success in combining EM and fractionation, which contributed in no small part to his receiving the 1974 Nobel Prize in Physiology or Medicine along with Claude and Christian de Duve. JCB

Claude, A. 1943. *Science.* 97:451–456.
Palade, G.F. 1955. *J. Biophys. Biochem. Cytol.* 1:59–68.
Palade, G.F. 1956. *J. Biophys. Biochem. Cytol.* 2:85–97.
Palade, G.F., and P. Siekevitz. 1956a. *J. Biophys. Biochem. Cytol.* 2:171–200.
Palade, G.F., and P. Siekevitz. 1956b. *J. Biophys. Biochem. Cytol.* 2:671–690.
Porter, K.R. 1953. *J. Exp. Med.* 97:727–750.
Warner, J.R., et al. 1962. *Science.* 138:1399–1403.