CC/NUMBER 48
NOVEMBER 26, 1984

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Dallner G, Siekevitz P & Palade G E. Biogenesis of endoplasmic reticulum membranes. I. Structural and chemical differentiation in developing rat hepatocyte. *J. Cell Biol.* 30:73-96, 1966.
[Dept. Cell Biology, Rockefeller Univ., New York, NY]

This paper and the accompanying paper[1] used the endoplasmic reticulum (ER) membranes in livers of newborn rats as models for membrane biogenesis. The investigation led us to the conclusion that new membranes are not synthesized *de novo* as one unit, but that the various enzymes are added at an individual rate in order to complete the membrane. Also, several components that are synthesized in the rough ER membranes are subsequently transferred to the smooth ones. [The *SCI*® indicates that this paper has been cited in over 565 publications since 1966.]

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September 21, 1984

"Considering the immense developments in our knowledge of lipid and protein structure, conformation, and synthesis in just the last 10 years, it is not easy to go back even farther and recount the problems involved in studies of membrane biogenesis in the mid-1960s. Most of the ideas about how membranes are synthesized were speculative then, and the experimental observations were limited. I arrived in New York on the *Queen Elizabeth I* to start postdoctoral studies at Rockefeller University (Institute, at that time). I met with Palade and Siekevitz on my first day at Rockefeller, and they told me that a week earlier they had done an experiment to test some ideas that would be a suitable starting point for me. They had bought a few pregnant rats, studied electron micrographs of the livers of the newborn rats, and measured glucose-6-phosphatase activity on isolated liver microsomes. The amount of membrane observed had increased directly with the enzyme activity. This was a system obviously suitable for analyzing membrane biogenesis.

"The experiments I performed were expensive and not so easy. I ordered and obtained 15 pregnant rats for every experiment. These rats had been mated for delivery on a defined day. There was, however, some discrepancy between my rhythm and that of the rats. Each delivery was spread out considerably but concentrated somehow in the nighttime hours. Since most of the important biological changes in this system occur just after birth, I had to collect a sufficient number of newborn rats to start an experiment. My re-education from a pathologist to a gynecologist took place during the endless nights when I walked up and down 66th Street between First and York Avenues (between my home and the laboratory) to look at my rats and estimate the approximate time of delivery. I would walk home for a short rest several times during the night. My wife would wake up sometimes and ask in a sleepy voice: 'Are you coming or going?'

"Our efforts yielded highly rewarding results, which is not always the case in research. I learned a great deal about the morphological, chemical, and enzymic pattern of the developing endoplasmic reticulum (ER). The ensuing paper contained a description of the isolation of rough and smooth microsomes that is widely used even today. The fact that many of the membrane components are synthesized in the rough ER before transport to the smooth ER was interesting *per se*. But this was a minor finding in comparison with the main conclusion that biological membranes are not synthesized *de novo* as a whole, like the ones obtained in reconstitution experiments.

"Our work indicated that individual proteins have individual turnover times and that they are placed in and removed from the membrane individually to construct the final product. We suggested the principle that membranes are synthesized in a 'multi-step process,' contrary to the hypothesis of a one-step assembly of a homogeneous membrane. Our hypothesis, which has been substantiated during the subsequent years of experimentation, is the reason for the frequent citation of this paper.

"Time has passed and I am no longer working in this particular field, but I have followed closely the immense development that has taken place in the last decade.[2-4] This work provided me, a postdoc from another continent, with the great opportunity to encounter the atmosphere and the people of Rockefeller Institute, which have contributed so richly to innovation and achievement in cell biology research."

1. **Dallner G, Siekevitz P & Palade G E.** Biogenesis of endoplasmic reticulum membranes. II. Synthesis of constitutive microsomal enzymes in developing rat hepatocyte. *J. Cell Biol.* 30:97-117, 1966. (Cited 520 times.)
2. **Blobel G & Dobberstein B.** Transfer of proteins across membranes. I. Presence of proteolitically processed and unprocessed nascent immunoglobulin light chains on membrane-bound ribosomes of murine myeloma. *J. Cell Biol.* 67:835-51, 1975. (Cited 1,435 times.)
3. **Sabatini D D, Kreibich G, Morimoto T & Adesnik M.** Mechanism for the incorporation of proteins in membranes and organelles. *J. Cell Biol.* 92:1-22, 1982.
4. **Schatz G.** How mitochondria import proteins from the cytoplasm. *FEBS Lett.* 103:203-11, 1979. (Cited 110 times.)

