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Friend D S & Farquhar M G. Functions of coated vesicles during protein absorption in the rat vas deferens. *J. Cell Biol.* 35:357-76, 1967.
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The role of coated vesicles during horseradish peroxidase absorption was investigated by electron microscopy and cytochemistry. The results demonstrate that (a) this epithelium absorbs protein from the lumen, (b) large coated vesicles transport protein to lysosomes, and (c) some small coated vesicles move hydrolytic enzymes from the Golgi region to multivesicular bodies. [The *SCI*® indicates that this paper has been cited in over 710 publications since 1967.]

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"After completing two rich years as a postdoctoral fellow in Don Fawcett's department developing an ongoing love for microscopic precision and beauty, I sought Marilyn Farquhar in the department of pathology at the University of California, San Francisco, to have me for a third fellowship year. I wanted to learn enzyme cytochemistry at its best. I had been counseled on both coasts that descriptive microscopy had had its heyday: to be a contributor to the burgeoning field of cell biology, my dream, I must develop skills as an experimentalist. Cytochemistry, enjoyably tasted in OsO_4 impregnation studies,[1] was the type of tool I wished to master. The standards of excellence, ambience, and contemporary thinking in Marilyn's lab excited me.

"I brought with me some knowledge of using horseradish peroxidase (HRPase) as a tracer—then unpublished[2] know-how that Morris Karnovsky imparted to me. The stage for something exciting to happen was almost set—the facilities, laboratory knowledge, encouragement, the direction of a sound experimentalist, a new tracking procedure, and the freedom to work on a problem of my choice—a special delight granted me throughout my training. Two simple questions nagged me: was the epididymal epithelial cell absorptive? And if so, why did it have such a large Golgi apparatus?

"To begin, I infused HRPase into the lumen of the vas deferens trying to get retrograde flow to study its uptake by epididymal principal cells. Sometime between the sixth and thirteenth repetition of just-about-exactly this same experiment, I addressed myself to the equivalent question in the vas deferens. The thirteenth through the eighteenth repetitions all worked well: the cells took up the tracer in large, coated invaginations and vesicles. Comparing images from varying intervals indicated their direction and destination. Our improvements of the cytochemical and ancillary electron microscopic techniques for TPPase and ACPase, introduced by Alex Novikoff, Sidney Goldfischer, and Bob Smith, yielded comparable data on the flow of small coated vesicles. At that point, I began to write my findings, but had a hurdle to overcome: I did not fully grasp the quantitative relationship between two sets of vesicle-flow. The problem was resolved one sunny afternoon when George Palade patiently listened and intensely looked at all my data; then said one word—*count*. I counted the two vesicle populations at the different intervals and thereby cemented a relationship between them—a key to the success and popularity of the study. In addition to being among the first clearly illustrated and interpreted cytochemical studies of absorptive endocytosis, it was the first documentation of distinctive subsets of coated vesicles and an endosome compartment (the MVB), foreshadowing the now extensively explored areas of receptor-mediated endocytosis and membrane flow."[3-5]

1. **Friend D S & Murray M J.** Osmium impregnation of the Golgi apparatus. *Amer. J. Anat.* 117:135-50, 1965. (Cited 125 times.)
2. **Graham R C & Karnovsky M J.** The early stages of absorption of injected horseradish peroxidase in the proximal tubules of mouse kidney: ultrastructural cytochemistry by a new technique. *J. Histochem. Cytochem.* 14:291-302, 1966. (Cited 4,385 times.)
3. **Farquhar M G & Palade G E.** The Golgi apparatus (complex)—(1954-1981)—from artifact to center stage. *J. Cell Biol.* 91:77*s*-103*s*, 1981.
4. **Roth T F & Woods J W.** Fundamental questions in receptor-mediated endocytosis. (Marchesi V T & Gallo R C, eds.) *Differentiation and function of hematopoietic cell surfaces.* New York: Liss, 1982. p. 163-81.
5. **Bainton D F.** The discovery of lysosomes. *J. Cell Biol.* 91:665-765, 1981.

