

Inner Workings: Protein secretion

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In 1978, researchers had established that certain proteins in eukaryotic cells were secreted and that these proteins were produced in the endoplasmic reticulum and moved through the Golgi apparatus and into secretory vesicles that fuse with the cell membrane, releasing the proteins out of the cell. However, nobody had any idea how the cell actually orchestrated this process, let alone what genes were responsible.

It was a crucial question. Secretion underlies the transfer of signals between neurons. Many cancers have disruptions in the process of secretion that contribute to metastasis. “It’s absolutely fundamental to how eukaryotic cells work,” says Peter Novick, cell biologist at the University of California, San Diego. It was work on this question that won Randy Schekman of the University of California, Berkeley, the 2013 Nobel Prize for Physiology or Medicine. He shares the prize with James E. Rothman and Thomas C. Südhof. Novick was a student of Schekman’s, producing one of

the papers cited by the Nobel committee in awarding the prize (1) and isolating the first yeast strain with a mutation in its secretory pathway.

In this page from Peter Novick’s notebook, he shows the data that clinched the discovery, proving that the mutant strain accumulated enzymes inside the cell that it normally would have secreted past the membrane. The picture on the left is a measurement of the enzyme gathered from whole, intact cells of the mutant, known as *sec1-1*, and a control strain, 21801A. This figure represents secreted protein, showing only what is accessible at the cell surface. The graph on the right, in contrast, is a measurement of the contents of the cells’ interior; Novick took small samples from the cultures at each time point and removed the cells’ walls, leaving behind just what was inside for measurement.

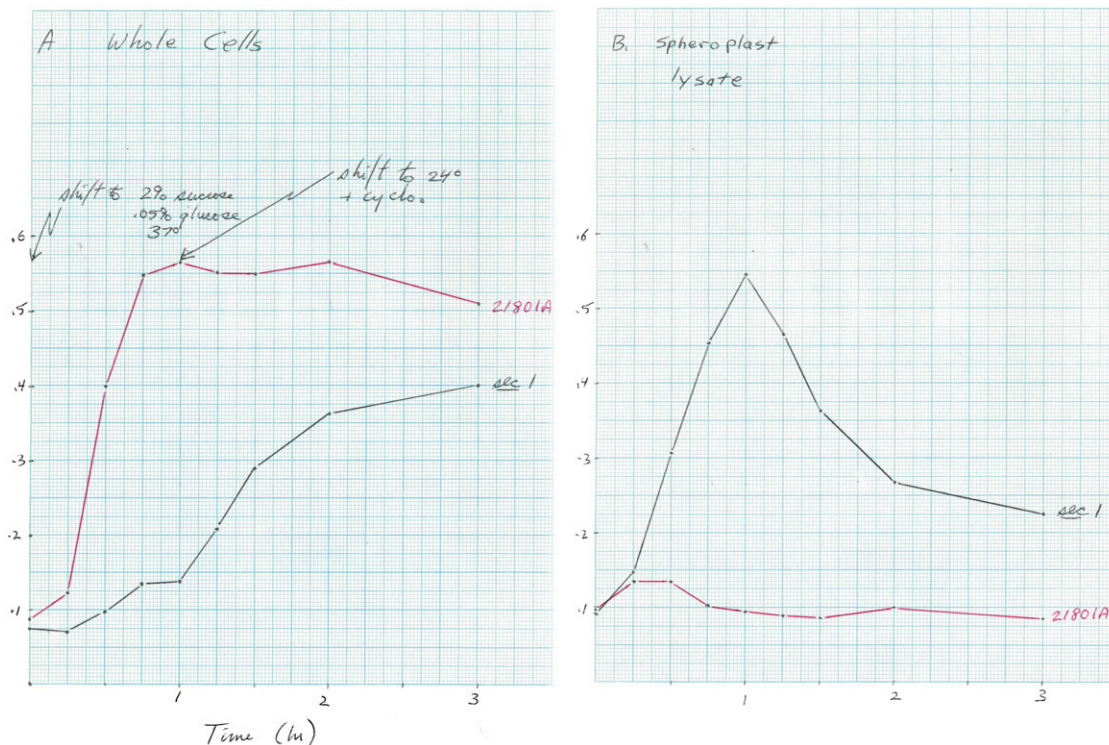
Because of how the researchers selected their mutant strains, the mutant behavior was only expressed at elevated temperatures.

In the experiment, the researchers exposed cells to elevated temperature for the first hour and then shifted back to normal temperature. During the elevated temperature phase, the mutant shows little secretion of protein, but the protein accumulates inside. Once the temperature restriction is removed, the protein leaves the cell again.

“I was very happy,” Novick said. “It’s what we were looking for but there were so many ways that it might have been impossible.” Schekman, Novick, and others went on to isolate hundreds more mutants. “I’ve never gotten a better mutant than that, that’s more picture perfect. The Sec1 protein has turned out to be very important.”

How did this paper—his first publication—rank among his life’s work thus far? Says Novick, “This is definitely at the top. It just opened up a whole new field. I’m still working on extensions of what I started with that line of research.”

1 Novick P, Schekman R (1979) Secretion and cell-surface growth are blocked in a temperature-sensitive mutant of *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 76(4):1858–1862.



Logbook image courtesy of Peter Novick.