

A Unique Discovery: Advancing Scientific Knowledge at PSC

by Marcia L. Santore

Sometimes the most interesting discoveries are made while looking for something else.

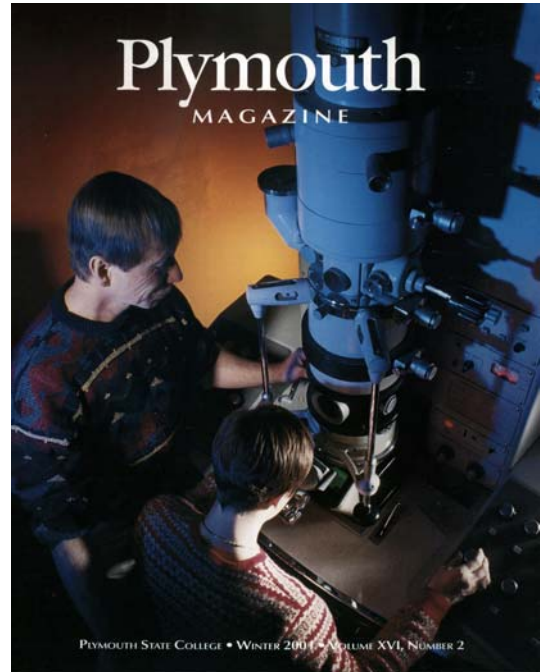
Fred Prince, professor of biology in PSC's Department of Natural Sciences, was continuing his research on the development of steroid-producing cells (reported in *Plymouth Magazine*, Winter 1999), when he made a fascinating discovery about the mitochondria of those cells.

Mitochondria are among the tiny structures called organelles that exist within our cells and help them to function. Mitochondria have a complicated and unique biochemistry. They have been called the "powerhouse of the cell" because of their role in producing a molecule called ATP, which provides the energy we need to keep moving. Muscle cells, which need a lot of energy, can have hundreds of mitochondria, while relatively inactive cells have just a few.

In the early 1950s, scientists using electron microscopes observed the structures of mitochondria in both typical and steroid-producing cells. They determined that mitochondria have an outer membrane and an inner membrane, and that the inner membrane of a typical mitochondrion is constructed in deep folds (called cristae, meaning "crests") while the inner structure of a steroid-producing mitochondrion is made up of tiny tubules. For 50 years, the world assumed that they were correct.

It took electron tomography (a recent technological advance which uses a large, high-voltage electron microscope interfaced with computers to take images from many different angles, and combine them into complex, three-dimensional-looking images) to determine that the structure of typical mitochondria was quite different from what had been taught for the past 50 years. Cell biologists at San Diego State University and Carmen Mannella's group at Albany, N.Y., discovered that in a typical mitochondrion, the forms called cristae were not folds at all, but separate irregularly shaped plate-like structures attached by tubules to the wall of the inner membrane. This discovery confirmed papers based on serial sections and electron microscopy, published back in 1959 and 1966, which had been "buried in the literature" and not taken seriously.

The electron microscope in Boyd Hall on the PSC campus was built in the 1960s and brought to PSC after Prince's arrival in 1985, with the support of then-President Farell. Prince refers to it as an antique, joking "only a few comrades in Siberia still use this model." Nevertheless, it was while using this "antique" equipment that Prince made his discovery: it was time to re-evaluate the structure of steroid-producing cells as well.



For his research, Prince uses Leydig cells, the testosterone-producing cells found in the testes. The tissue samples were obtained during diagnostic work at his previous position at Children's Hospital in Columbus, Ohio. He has studied thousands of the two-dimensional, black-and-white images of these cells produced on the electron microscope. He favors actual looking over computer modeling, saying "I like to stay as far away from the computer as possible" for this kind of work.

Yes, he found tubules, as would be expected. But he also found cristae similar to the forms recently described by electron tomography. This was a new finding for steroid cells. Most striking, however, was the presence of cristae intimately associated with one another, forming "stacks." Prince calls these stacks "lamellar associations," explaining, "It's almost like an organelle within an organelle." Prince has reviewed hundreds of different types of cells in his career and is convinced that this structure is unique to steroid-producing mitochondria.

Unlike the recent research on typical mitochondria, which confirmed lost findings, Prince's discovery is absolutely new. Although the technology he is using has been available for decades, Fred Prince was able to detect something that had previously gone unrecognized.

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Prince published "Mitochondrial Cristae Diversity in Human Leydig Cells: A Revised Look at Cristae Morphology in These Steroid-Producing Cells" in *The Anatomical Record* in 1999. This work, as well as micrographs showing that "routine" electron microscopy can show cristae structures of typical mitochondria in images comparable to those produced by the new electron tomography, was presented at the Frontiers of Mitochondrial Research conference in Albany, N.Y., in September 2000.

His cell-biologist colleagues are intrigued: *The Anatomical Record* published Prince's paper only five months after his initial submission—very quickly for a peer-reviewed scientific journal. Mannella has offered the use of the electron tomography equipment available at Albany and preliminary studies have begun.

Students in Prince's cell biology course have shared in the excitement of revising our view of cell structure. For over a decade, PSC biology students have been taking the fall cell biology course, with a smaller group enrolling in a spring semester course in electron microscopy. "An electron microscopy course available to undergraduates is rather unusual," says Prince, who has been teaching this course since 1988. "It is a graduate level course at the vast majority of major institutions ... I have been told that most Ivy League schools do not offer this to undergrads ... I think it is safe to say it is a relatively unique opportunity for an undergraduate student!" Prince accepts only four students at a time into this intensive techniques course each spring. These students have gone on to graduate work in physiology, cell biology, biophysics, optometry, veterinary medicine, dental school and medical school at major universities around

the country. Others have gone on to work in pathology labs, biotech labs or as high school teachers.

“For years I’ve noticed that students become inspired to pursue graduate programs and careers in medical science once they see that science is not static, but is very dynamic, constantly refining our view of how cells work and at times is revolutionary,” says Prince. “Science is slowing putting together the pieces of a great mystery.”

So, what does it all mean? At this point, there is no telling where research such as Prince’s might lead. “For 50 years we’ve had this simplistic model,” he says, adding “structure relates to function ... the role of mitochondria in energy production, as well as steroid synthesis, will only be understood when the biochemical studies are integrated with the new structural paradigm.”

There are numerous possibilities. Prince explains, “This new wave of mitochondrial research has included topics such as their involvement in, perhaps control of, a phenomenon termed apoptosis (programmed cell death). This will have implications for cancer, autoimmune disease and neurodegenerative disease. This was a major topic at the recent mitochondrial conference.” Another fascinating area of current research is the use of mitochondrial DNA to study human evolution, including issues of ancient migrations.

Mitochondrial research will continue to provide insights into cell biology and human medicine. And who knows? PSC students working with Prince may just be the ones to find the next piece of the puzzle.