Stephen Doxsey

If his teacher in Advanced Placement (AP) Biology had a first name Stephen Doxsey can't recall it, but it was Mr. Tulve who made all the difference. Dragging his AP class to ponds on field trips or into the lab to work up the results, Mr. Tulve gave Doxsey the notion that biology could be his future, even if it took him a decade to figure it out. In the interim, Doxsey competed in high school pole vaulting, intercollegiate diving, and serious softball. He earned a biology degree at the University of Connecticut, having greatly enjoyed a class on electron microscopy (EM) but without having been caught up in lab life.

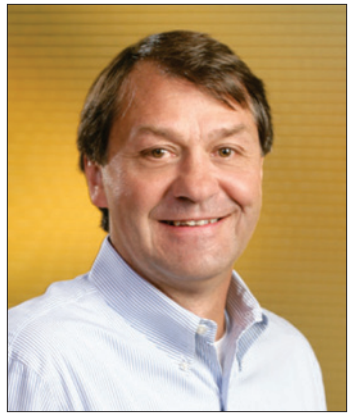
At loose ends after graduation, Doxsey went to Boston on a whim with a high school chum who was looking for something in accounting. Doxsey thought he'd try lab work. He turned up at Harvard Medical School (HMS) in a heavy corduroy suit one hot summer afternoon and went door-to-door, asking if anyone needed a lab tech with minimal EM experience. The neurobiologist Elio Raviola took him on. Two years later, Doxsey was in the midst of a complicated freeze fracture set-up for Raviola when Don Fawcett came into the EM facility. Seeing that Doxsey was busy, Fawcett turned to leave, only pausing at the door to ask over his shoulder if Doxsey would like to go to Africa. Doxsey ran down the hall after him, shouting, "Yes! Yes!"

Most of all, Doxsey worked, one-on-one, with Fawcett. "That's what transformed me into a scientist," he says.

Fawcett, who was a pioneer in the application of EM to cell biology (and the first president of the ASCB), had decided to step down as chair of the Anatomy Department at HMS. He was taking a position at a state-of-the-art research station in Kenya, funded in part by the World Bank, to study cattle diseases. For the local Masai and Kikuyu people, who have much of their culture (and wealth) tied up in cattle, East Coast Fever was a constant threat. The parasite vector was the tick *Rhipicephalus appendicultus.* Over the next two years, Doxsey became particularly intimate with the tick's salivary gland. Doxsey was fascinated by the tick's evolutionary resourcefulness—its self-made chisels, tanning agents, skin-dissolving enzymes, and anticoagulants. "I still have a love for ticks," he admits, "even though I had a deer tick on me the other day. They just have this incredible [biological] repertoire."

Outside the lab in Kenya, Doxsey was having the time of his young life. The research center was in the country far enough from Nairobi that he could live in a traditional Kikuyu community but close enough for softball games on Saturday with the American consular staff. His Western salary gave him an incredible standard of living and the means to explore East Africa's legendary wildlife reserves. Most of all, Doxsey worked, one-on-one, with Fawcett. "That's what transformed me into a scientist," he says. Fawcett gave him a nonstop course on EM, cell biology, evolution, parasitology, mammalogy, East Africa, running a research lab, and wildlife photography. Fawcett, who was an (otherwise) nonpracticing MD, even gave him his shots. Says Doxsey, "After that experience with Fawcett, there was no doubt where I was going—research."

Graduate school was Yale. Cell biology was still so new a discipline that Yale had a program, not a department, in 1982. The Yale program featured some of the field's founders, such as George Palade and Marilyn Farquhar, plus rising stars such as Ira Mellman and Ari Helenius. Sandy Schmid and Judy White were postdocs in the all-but-officially merged "Mel-enius lab" where Doxsey arrived as an older-than-average grad student with an exotic résumé. White, now at the University of Virginia, remembers Doxsey as a great friend and a formidable bench partner. "An absolutely incredible experimentalist, one of those, I say, whose hands should be insured by Lloyds of London," declares White. "Steve was a no-nonsense, unpretentious person who got the job done and was—and still is—always excited by the science."



Stephen Doxsey

Delivering Drugs by Virus

Schmid, now at The Scripps Research Institute (and current ASCB president), recalls Doxsey's Yale thesis project as extreme cutting-edge science. Doxsey used influenza virus hemagglutin to deliver anti-clathrin antibodies into cells to inhibit endocytosis. This was at a time when clathrin was exotic, endocytosis little understood, and the use of viruses for drug delivery unheard of. "This was completely out-of-the-box, new thinking," says Schmid. "People only now are trying to use viruses for drug delivery, but Ari and Steve were doing this 25 years ago."

Combine his passion for action sports like rock climbing and skydiving with Doxsey's scientific progression from parasites to viruses to centrosome proteins, says Schmid, and you will understand what drives Doxsey's career. "What typifies Steve is that he's incredibly adventuresome, both scientifically and personally."

"[Doxsey is] an absolutely incredible experimentalist, one of those, I say, whose hands should be insured by Lloyds of London," declares White.

Helenius concurs. Doxsey's PhD advisor, Helenius was just starting at Yale when Doxsey joined his lab. "Steve was amazing at getting things done, particularly anything to do with morphology or EM," recalls Helenius who is now at Eidgenössische Technische Hochschule, the Swiss Federal Institute of Technology in Zurich. "He was a complete natural at that."

The only question for his advisor was whether Doxsey would make the transition from super technician to independent scientist, Helenius explains. Beyond the academic fundamentals, Doxsey needed to develop a scientific frame of mind. That Doxsey succeeded so well, says Helenius, had as much to do with the other grad students and postdocs in cell biology as anything he taught Doxsey. Actually the only thing Helenius believes that he might have taught Doxsey was how to play squash. He showed Doxsey the basics in a dusty, hot basement court on campus. "It didn't take Steve long," Helenius recalls of the squash lessons, "before he was winning every game."

Doxsey went on to a postdoc with Marc Kirschner at the University of California, San Francisco, and a ranking in Bay Area squash leagues. Besides playing tournaments, climbing the north tower of the Golden Gate Bridge, and teaching winter wilderness survival courses, Doxsey discovered pericentrin, a bedrock protein of the centrosome complex that controls cell division. Kirschner, who is now at HMS, recalls that Doxsey's breakthrough grew from an unusual observation—antibodies taken from a patient with the autoimmune disorder scleroderma stained something in the centrosomes of cultured cells. The same antibodies also stained an unidentified protein in early-stage mouse blastomeres, which don't have centrioles, the barrel-shaped structures that orient the mitotic spindle. A protein that preceded centriole formation looked interesting, and Doxsey went after it using the cumbersome technology of the day. Kirschner explains, "The present generation of students who are used to looking these things up [in genomic databases] may not appreciate what a difficult job it was to get the full sequence of this protein. The story is of historical interest now but it was way ahead of its time, and basically Steve did the whole project."

Ambitious Things

The result was pericentrin. Says Kirschner, "We discovered it. We named it. We cloned it. And we understood its structure and how it formed this network of filamentous material which became the scaffold on which a lot of microtubule nucleating activity took place." Looking back, Kirschner said Doxsey demonstrated considerable ingenuity and technical flair at the bench. "But it also took a certain kind of determination to succeed and persistence to follow all these connections," he adds. "That's part of Steve's character too. He likes to do ambitious things."

In the years since establishing his own lab in 1993 at the University of Massachusetts Medical Center (UMass Med) in Worcester, Doxsey has largely stayed with the centrosome while pursuing its biological implications ambitiously. Along with making basic findings on chromosome segregation, polyploidy, and tumorigenesis, Doxsey has worked on a variety of human diseases, including prostate cancer, scleroderma, and polycystic kidney disease, all tied to centrosome defects. Perhaps none is more startling than the connection between pericentrin and a type of primordial human dwarfism, Majewski osteodysplastic primordial dwarfism type II (MOPDII).

In 2008, Doxsey began exploring links between mutations in the human pericentrin gene and the severely stunted growth and other physiological characteristics typical of patients with MOPDII. The condition was not officially described until 1982, but its scientific history has been traced back more than a century to Lucia Zarate. At 20 inches in height and five pounds in weight, she may have been the smallest woman who ever lived. Zarate was a protégé of the great American fabulist, P.T. Barnum, who featured her on tour across two continents as the "Mexican Lilliputian."

[MOPDII] was not officially described until 1982, but its scientific history has been traced back more than a century to Lucia Zarate. At 20 inches in height and five pounds in weight, she may have been the smallest woman who ever lived.

In recent work presented in part at the 2010 ASCB Annual Meeting in Philadelphia, Doxsey reported that a pericentrin-null knock-out mouse developed by his lab shows features strikingly similar to primordial dwarfism in humans. This includes structural defects in the circulatory system that make heart attack and stroke a common cause of early death in people with MOPDII. Pericentrin-null mice exhibit a reduction in the number of cell divisions. They produce fewer of the stem cells and their progeny that give rise to the billions of cells needed to build an organism, Doxsey explains. Stem cell divisions are often controlled through the orientation of the plane of cell division. Positioning the plane of cell division and positioning the mitotic spindle is a known function of pericentrin. "It is easy to imagine how reduction in stem cell self-renewing divisions could decrease cell number in all tissues, leading to a smaller organism," says Doxsey.

Outdoorsy Family

Today Doxsey lives north of Worcester outside the tiny town of Sterling, MA, with his family: wife, Cindy Sparks, their 10-year-old twins, Will and Dylan, and 8-year-old daughter, Samantha, whom they adopted as a baby from Vietnam. Sparks is a lab manager at UMass Med, but she also teaches college biology, deals in antiques, and sells real estate. The Doxsey kids are all extremely outdoorsy, reports their father. They're keen on hiking, climbing, swimming, and diverse childhood sports. Doxsey is teaching them the rudiments of competitive diving in their backyard pool.

And then there is Mr. Tulve. About a decade ago, Doxsey began thinking again about that fateful AP Biology class at the Newburgh Free Academy, his public high school in New York's Hudson River Valley. Doxsey decided to call up the AP Biology teacher at North High School in Worcester and offer to host four of the 12 mandatory AP labs at UMass Med. The labs were a huge success. "They got to squeeze the frogs, stain some slides, and look through a decent microscope," Doxsey reports. The program has expanded to all four Worcester high schools (with two more area schools in the wings). Doxsey now recruits 20–30 of his PI colleagues at UMass Med to host the AP labs each year for a program that earned Doxsey the university's President's Public Service Award in 2007. "I guess it comes full circle," says Doxsey, "from Mr. Tulve right back to my laboratory." ■

—John Fleischman

Introducing... The New WICB Speaker Referral Service

Looking to diversify and expand your pool of excellent speakers and reviewers? The Women in Cell Biology (WICB) Committee offers a Speaker Referral Service for organizers of scientific meetings, scientific review panels, and university symposia/lecture series. Why? Diversity at the podium, or in the review process, often results in a more interesting and better outcome.

The WICB service offers *two processes* that make it easy for organizers, early in meeting planning stages, to receive a list of outstanding women in relevant field(s) to consider as invitees and reviewers. Please take a look at the new Speaker Referral Service at www.ascb.org/WICBspeakerref.html. ■