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A CONVERSATION WITH

Eric Betzig's Life Over the Microscope

By Claudia Dreifus

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In October 2014, the Nobel Prize in Chemistry went to three scientists for their work developing a new class of microscopes that may well transform biological research by permitting researchers to observe cellular processes as they happen.

One of the winners was Eric Betzig, 55, a group leader at the Janelia Research Campus of the Howard Hughes Medical Institute. On Thursday, the journal Science published a paper by him and his colleagues describing a microscope powerful enough to observe living cells with unprecedented detail — a goal he and others have spent decades pursuing.

I spoke with Dr. Betzig recently for three hours at his laboratory and office in Ashburn, Va., and again later by telephone. A condensed and edited version of the conversations follows.

Q. What makes these microscopes different from those most researchers use in their laboratories today?

A.The big problem with the standard optical microscope — that's the one in most biology labs — is that they don't magnify enough to see individual molecules inside a living cell. You can see a lot of detail, but it's 100 times too coarse for single molecules. With the more sophisticated electron microscope, you can get down to the molecular level. But to do that, you have to bombard your sample with so many electrons that you essentially fry it. This means you can't see a living process in real time.

What I and others have been trying to do is create microscopes that can image the building blocks within a cell. The goal is to link the fields of molecular and cellular biology, and thus unravel the mystery of how inanimate molecules come together to create life.

Are you a biologist by trade?

You know, I'm not comfortable with labels. I'm trained in physics but don't think of myself as a physicist. I have a Nobel Prize in Chemistry, but I certainly don't know any chemistry. I work all the time with biologists, but any biology I have is skin-deep. If there is one way I characterize myself, it's as an inventor. My father is that, too. He spent his life inventing and making tools for the automotive industry. I grew up around inventors.

When did the quest to build this microscope begin for you?

I started working on this in 1982 as a grad student at Cornell. By 1992, I had my own lab at Bell Laboratories. There, I built what's called a near-field microscope that worked, to a degree. But this instrument was still too difficult, slow and damaging to samples to be useful for biological research on live tissue. I became frustrated and quit both it and Bell Labs in 1994.

Shortly after that, two experiments I'd done at Bell with this machine sparked the idea that I published in 1995 and that would eventually lead to photoactivated localization microscopy — PALM — 10 years later.

Ten years? Why did it take that long?

Well, for one thing, I went through a very depressing period after leaving Bell. My then-wife and I had just had a baby. I stayed home as a house husband, trying to figure out what to do next. Should I go to med school? Become a gourmet chef? I didn't have any plan except to stop making microscopes.

Astonishingly, a couple of months after quitting, an insight came to me about how to make the microscope finally work. It came while I was pushing my child's stroller. The idea involved isolating individual molecules and measuring their distance. I wrote this up in a three-page paper, which would later be noted by the Nobel Committee as one reason for giving me the prize.

Funny thing about that paper: It wasn't much cited, probably only a hundred times in 20 years. That tells you something about the value of citations as a metric of impact.

For the next eight years, I worked in private industry, and I discovered it was even harder to succeed there than in science.

By 2004, I was in another personal crisis, and I looked up my best friend from the old days at Bell, Harald Hess. Harald had quit Bell a few years after I did. He was now working for a company that made equipment to test disk drives and was feeling unsatisfied. So we began trying to figure things out by taking trips to Yosemite and Joshua Tree and talking about what the hell we wanted to do with our lives.

I started reading up on all the developments in microscopy of the past decade. And that led to us to building, in Harald's living room, the microscope I'd envisioned while pushing my baby's stroller — PALM.

Were you pleased with what you built?

To a point. PALM had the limitations I mentioned earlier. By 2008, I became bored and frustrated with it, and started working on other types of microscopes. By then, I was at Howard Hughes and could work on anything that interested me. Here I developed the lattice light sheet microscope, which can image living cells at unprecedented speeds and often with no damage. But its resolution level wasn't any better than that of conventional microscopes.

I also worked on a highly advanced SIM microscope, which was begun by my Janelia colleague Mats Gustafsson, which would allow us to look at a sample in high resolution and at high speed. Mats occupied the office next to mine, and he was — I don't say this lightly — one of the most brilliant people I've met. Unfortunately, he was diagnosed with a brain tumor after falling off his bike on the way to work in 2009, and died in 2011.

When Mats died, there was still much work to be done to make his high-resolution form of SIM compatible with live imaging. After his death, I inherited much of his instrumentation and a few of his people. Since then, we've been working to make his higher-resolution instrument fast and noninvasive enough for live cells.

We believe we've done it. The result is a paper published in Science. We finally have the tool to understand the cell and the dynamics of its full complexity.

How has the Nobel affected your life?

It's disrupted my happy life quite a lot. I hate traveling, and you're constantly asked to give talks. I'm in a second marriage. I have young children, ages 2 and 5. The emails, the travel have kept me away from the two things I love the most: my family and my work. However, this is a problem of my own making. I'm learning to say "no" more often.

I mean, I'm a guy who's always been insecure, O.K.? You do feel more confident. On the other hand, insecurity always made me productive. These days, I sometimes want to slap myself and say: "You gotta keep pushing. This isn't the end. This is a chapter."