People & Ideas

Bruce Nicklas: Pioneering studies on spindle forces

Nicklas performed innovative studies on the forces that drive cell division.

By the 1960s, researchers had developed the microscopy techniques needed to observe and record live cells undergoing cell division. But the mechanisms used by the mitotic apparatus to faithfully distribute DNA into daughter cells remained mysterious.

Bruce Nicklas is responsible for many of the groundbreaking studies that helped sweep the veil of mystery away from chromosome segregation. By pulling on individual chromosomes with glass needles (1), Nicklas demonstrated the importance of spindle fiber tension for the onset of anaphase (2, 3), measured these forces (4), and showed how they alter the chemical state of kinetochores (5). Now an emeritus professor at Duke University, Nicklas cheerfully shared with us some stories about the surprises he uncovered in his life and work.

LOVE OF THE STRANGE

What hobbies did you have as a child?

I became interested in chemistry early on. When I was growing up in the early 1940s, plastics and polymers like nylon were invented in the United States. That made us a world leader in the sciences, particularly in chemistry. This captivated me, and I decided I was going to be a chemist. I didn't become interested in biology until much later.

When did biology first snag your attention?

I was a chemistry major during my first year in college. But then I took a course in quantitative analysis that I did not enjoy at all, and I actually dropped out of science for a while and considered becoming a philosophy major. Then, in my sophomore year—I can't remember why—I took a course on microtechniques in biology. What we did was fix tissues, slice them into thin sections, stain them, and look at them in a microscope. I think most people found this incredibly boring, but I loved it. I could sit all day and look down a microscope. I still can.

I decided pretty early on that I wanted to go to graduate school, and I first went to Western Reserve University (now Case Western Reserve) in Cleveland, Ohio. It was close to where I grew up, and there were some interesting people there. But a professor I knew told me, "You should go to Columbia University. There are some wonderful people working there."

So I transferred to Columbia, and she was right. It was really wonderful. My supervisors were Franz Schrader and his wife, Sally Hughes-Schrader. They were inspirational, yet they were the kind of people who didn't assign thesis topics. What you worked on had to come from you.

What did you choose to work on?

I looked at strange kinds of cell divisions in the embryos of certain insects in which chromosome elimination occurs. In these animals, at one or two particular divisions in early embryogenesis, all of the chromosomes line up at the metaphase plate and then begin to move toward the poles, but only a few complete the entire trek. All the rest are left behind and do not get included in the daughter nuclei that are formed. Eventually, these left-behind chromosomes degenerate.

> "I think most scientists like things that are strange."

This happens in more than one insect group, but I worked on a primitive gall midge that never forms an adult. The reproductive life cycle of these animals had already been well described, and it was known that the female larvae have an ovary in which the embryos begin, without fertilization, to develop inside the mother. Eventually, the mother will be—this is a little touchy—consumed by the larvae as they grow up inside her. It is very strange, and I liked that. I think most scientists like things that are strange.

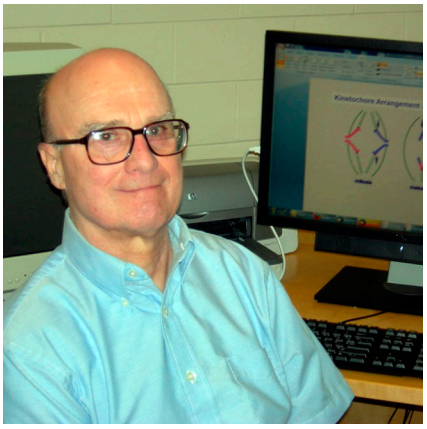

PHOTO COURTESY OF DR. BETH SULLIVAN

Bruce Nicklas

A MOVING EXPERIENCE

After working on this, did you do a postdoc?

No, I didn't. At that time, in late 1958, postdocs were sometimes done but not always, and I already knew what I wanted to do next. I took a job at Yale and, after one more paper on gall midges, began to do what I really wanted to do, which was to work on living cells.

I wanted to study cell division in grasshopper spermatocytes. I knew from work that was done in the 1920s that these are very large cells with big, juicy chromosomes. Unlike tissue culture cells, grasshopper spermatocytes do not round up during division, so you can very clearly see what's going on inside them. I wanted to measure the forces that produce the movement of chromosomes in anaphase.

I followed in the footsteps of Mitsuki Yoneda, who had developed a way of measuring the forces exerted by cilia using a very thin glass needle. I learned how to make these needles, how to insert them into the cells, and how to pull on a chromosome in anaphase. I thought that if I could apply just enough force to stop a chromosome moving, I could measure the bending of the needle and determine the force. But actually, I didn't get around to doing that experiment for another 15 years or so, because I got distracted.

Text and Interview by Caitlin Sedwick
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With what?

I found I could go in and pull chromosomes off the spindle and that they would reattach. You see, once a chromosome has been taken off the spindle, its spindle fibers are broken, and it can be put anywhere in the cell. I discovered I could change the angle of the chromosome with respect to the spindle and, in this way, determine to which spindle pole the chromosome would form a new attachment. I could understand the relationship between position and the interaction with the spindle.

I well remember the day I first observed this. It is the most moving thing—that's not intended to be a pun—I ever experienced in my life. Chromosomes, once detached from the spindle, spontaneously form a new attachment by capturing microtubules that happen to be in the vicinity of the kinetochore… I still think that's a very remarkable feature of cells.

Anyway, I just had too much fun pulling on chromosomes, so it took me a while to get back to my original idea of measuring the forces during anaphase. They turned out to be unexpectedly large and therefore likely due to motor proteins such as myosin or dynein.

> "I just had too much fun pulling on chromosomes."

You also addressed the importance of tension in the mitotic spindle…

Yes, and that's probably led to more work by other people than anything else I've done; it led to the suggestion that tension would determine stability.

All the interactions between chromosomes and the spindle are random. If one kinetochore becomes attached at one pole and its partner becomes attached to the opposite pole, then things will work fine. Well, as it happens, only in this case is the chromosome under tension. And it is that tension that stabilizes the appropriate attachment of chromosomes and thus determines their equal distribution in the ensuing anaphase. That was a great pleasure to me. I'd expected something much more complicated.

PLEASANT SURPRISES

You spent most of your career as an independent researcher at Duke…

That's right. I started out at Yale, but then I got an offer from Duke that included tenure. I would have had to wait awhile to be considered for tenure at Yale, and I didn't want to fuss about positions. So I happily went to Duke, and, I must say, it's been a great blessing. My wife, Sheila, who's a developmental biologist, had a lovely job at what became the Cell Biology Department in the medical school, while I was in what was then Zoology but later became the Biology Department in the liberal arts school.

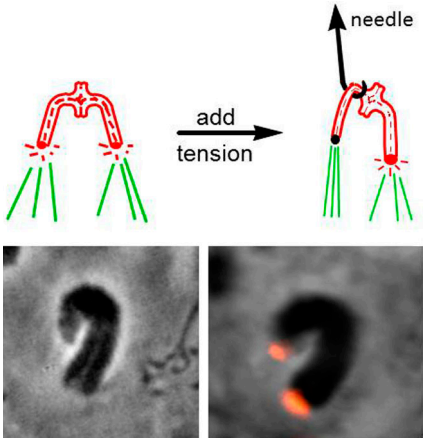
What do you do now that you are retired?

I thought I'd be a researcher until they put me in the ground, but I've been retired now for five years, and I've really enjoyed it. I come into my office every day except Saturday (which is farmers' market day) and kibitz with active researchers about experiments they're doing. And Sheila and I have become really interested in old movies, so typically—well, let's say four or five times a week—our afternoons are spent watching some old movie or other. We enjoy that a lot. We are probably the heaviest users of Netflix hereabouts. [Laughs]

I must say, though, that one of the things I miss at least as much as research is advising students. I was good at it.

What kind of advice did you give to students?

Take a humanities course—say, a good course in medieval history or the fine arts. When I was an undergraduate and a graduate student, science was the only thing I was interested in. But then I discovered modern art and, later on, Renaissance art. It just added so much to my life. It never took anything away, as I'd feared it would. So, I encourage people to find interests outside of science, just because it's so life-affirming.



NICKLAS, R.B., S.C. WARD, AND G.J. GORBSKY. 1995. *J. CELL BIOL.* 130:929-939.

Phosphorylation (red, bottom right) at one kinetochore is altered when a glass needle pulls on a meiotic chromosome whose kinetochores are both attached to the same pole. The kinetochore under tension shows less phosphorylation of kinetochore proteins.

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