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From Telomeres to the Origins of Life

By CLAUDIA DREIFUS

BOSTON — The October night before he learned he had won the 2009 Nobel Prize in medicine, the biochemical researcher Jack W. Szostak says he slept like a log.

“I wasn’t going to lose a night’s sleep because of work I’d done in the 1980s,” Dr. Szostak, 58, said with a laugh during a recent two-hour interview at his laboratory at Massachusetts General Hospital. “It was old work.”

That “old work,” for which he had already won the Lasker Prize, was to help identify the nature and biochemistry of telomeres, the tips at the ends of chromosomes. Understanding them may be the key to unlocking the mysteries of cancer and cell aging. An edited version of our conversation follows.

Was telomere research your life’s work?

It was somewhat of a side project. Before I began working on telomeres, I’d been studying DNA recombination. What do cells do when they see a broken piece of DNA? Cells don’t like such breaks. They’ll do pretty much anything they can to fix things up. If a chromosome is broken, the cells will repair the break using an intact chromosome. That process is called recombination. And that’s what I was looking at.

Now, telomeres: They are the ends of chromosomes, the caps, and they don’t recombine. One day in 1980, I heard Liz [his colleague Elizabeth H. Blackburn] at a conference talking about how telomeres behaved. It was the contrast between the DNA she was working with and the material I was studying that caught my attention. I wanted to understand what was going on. So I wrote Liz right afterward.

What did you discover together?

We figured out what was going on at normal chromosome ends. We figured out the underlying biochemistry and showed that lots of different organisms use that biochemistry. We figured out that there was an enzyme, telomerase, that adds DNA to the ends of chromosomes to balance out the DNA that is naturally lost as cells grow.

Afterward, as people in the field began to see how important it was, telomere research just took off. It became clear that the loss of DNA from telomeres might have something to do with aging. Subsequently, it's turned out that in almost all cancers, telomerase is turned on so those cells grow indefinitely. Of course, it's very nice that work we did so long ago turned out to be important! But the truth is my work has gone off in several different directions.

What do you study now?

The origins of life. In my lab, we're interested in the transition from chemistry to early biology on the early earth. Let's go back to the early earth — let's say probably some time within the first 500 million years. And let's say the right chemistry that would make the building blocks of life has happened and you have the right molecules with which you can spark life. How did those chemicals get together and act something like a cell? You want something that can grow and divide and, most importantly, exhibit Darwinian evolution. The way that we study that is by trying to make it happen in the lab. We take simple chemicals and put them together in the right way. And we're trying to build a very, very simple cell that might look like something that might have developed spontaneously on the early earth.

How far have you gotten?

Maybe I can say we're halfway there.

We think that a primitive cell has to have two parts. First, it has to have a cell membrane that can be a boundary between itself and the rest of the earth. And then there has to be some genetic material, which has to perform some function that's useful for the cell and get replicated to be inherited. The part we've come to understand reasonably well is the membrane part. The genetic material is the harder problem; the chemistry is just more complicated. The puzzle has been understanding how a molecule like RNA can get replicated before there were enzymes and all this fancy biological stuff, protein machinery, that we have now in our cells.

It's very unusual for a researcher who's made big breakthroughs in one scientific area to move into a completely different one. Why shift fields?

Because by the mid-1980s, it became clear what the questions with telomeres were and that they were going to be addressed perfectly well by others. I'm not the sort of person who likes a lot of competition. I particularly don't like the feeling that if I wasn't around doing certain work, it wouldn't make any difference. If it's going to be done anyway, what's the point, right?

For about a year, I actually took courses here at Harvard, looking for something else to work on. I looked at cognitive neuroscience, which is incredibly fascinating, but seemed way too hard. RNA structure appealed because it could be key to understanding the beginning of life on earth.

You've now been working on this problem for a quarter of a century. Do you ever grow weary of it?

No. No. Because this isn't a monolithic question where there's nothing interesting until you get to the end. In fact, the question breaks down into maybe a dozen smaller questions. Each has interesting parts. Eventually it will all fit together.

For instance, we've made progress on the question of how you make a primitive cell membrane. Others had showed how a common clay mineral, montmorillonite, might have played a role in helping to make RNA. Our lab showed how it could help membranes to form and bring the RNA into the membrane.

You try to actually make life in your lab. In essence, you're trying to prove evolutionary theory in a petri dish. How do religious fundamentalists feel about your work?

After that work on clay was published, we got a lot of e-mail from fundamentalists: "Oh, this is so wonderful. We are so happy that you've shown that it's just like it's written in the Bible or the Koran." In Genesis, it begins with clay.

Growing up in Canada, were you one of those children who did chemistry experiments in the kitchen?

We did things that were ridiculously dangerous. But they were exciting, too. I remember in 1967, when there was that terrible fire on NASA's Apollo 1 rocket that killed three astronauts, my father made pure oxygen and we lit this tiny cup and burned it. Suddenly, we had an unbelievable jet and a fire. You just could see exactly what had happened.

There's no way that you could do that at home today. I guess a lot of kids lost eyes and limbs with the older stuff. The concern is understandable. Still, a kid needs to see something happening to get excited. My younger son, who is 11, likes chemistry. It's a challenge to find anything exciting for him to try out.

Did the Nobel Prize change your life?

Nothing significant is any different. More people come up to me at conferences and want to have their picture taken with me. I wouldn't say it's any easier for us to get our papers accepted or to get grants.

The thing about the Nobel ceremony is that for a whole week, you get treated like a superstar. You get driven everywhere. You have minders who always make sure you get where you're going. And you always get into the back seat of the limo. So we were told this story about one Nobel laureate who flies home, and he goes to get his car and he gets into the back seat and he just waits.