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A Conversation with Elizabeth Blackburn

Elizabeth Blackburn has spent much of her professional life exploring the far ends of chromosomes. In 1976, she discovered that they were capped by strange repeating sequences of DNA. Her discovery of telomeres and, with colleague Carol Greider, of the telomere-making enzyme telomerase, would draw her to the center of a now-burgeoning field, telomere biology, earn her numerous awards, and, eventually—as a famously appointed-and-dismissed member of President George W. Bush's Advisory Council on Bioethics—a kind of scientific celebrity. Blackburn, the Morris Herzstein professor of biology and physiology in the department of biochemistry and biophysics at the University of California, San Francisco (UCSF), was born on November 26, 1948, in Hobart, Tasmania. She is the subject of a recent and critically acclaimed biography, *Elizabeth Blackburn and the Story of Telomeres*, by Catherine Brady *(1)*, a story that begins at the far end of the world. She spoke with me from her home in California.

Catherine Brady describes you as a young woman of 17 living in Tasmania—shy with boys but very passionate about science. You were infatuated with amino acids and felt they had a "teasing beauty." What captured your imagination?
I'd just always been very interested in biology and the idea that there would be a chemistry behind it was captivating for reasons I can't explain. I guess I got the feeling that it would be a real explanation for what underlay a lot of biology. But I also liked the shapes and I liked the names.

Is it true that you plastered your bedroom walls with pictures of amino acids that you drew?
Absolutely. Butchers used to wrap meat in big white rolls of paper and so I got some of that.

You must have some artistic ability.
I used to love drawing when I was a kid, of naturalistic things. I didn't do abstract things.

Your parents were both general practitioners and presumably somewhat familiar with science. Yet it sounds like you felt the need to protect or hide your love of science.
Not from my parents—they were very encouraging. I remember I got a microscope for Christmas once. I was so excited. They were very encouraging of that. Among my peers, that wasn't a necessarily acceptable thing. So I didn't talk about it.

Did you actually have to suppress this passion? I ask this because in the early part of her book, Brady portrays a tension in you between a very strong inner will and an external pressure to appear feminine.
It's a little sad to examine oneself but I think she kind of nailed it. When I try to think about it, that seems real to me.

So you felt some pressure to feel more demure?
Yes, that's right. I remember I had this chemistry set out in this little garden shed and I thought that was just the most wonderful thing. But it wasn't the kind of thing I would talk about with my school friends. And I remember I had little guinea pigs and one of them had little babies. They were born very mature looking, not bare, they had fur on them. I put them in my hand and showed them to one of my friends and it was like—aarrghh! I thought they were so cute but she saw them as little vermin.

That reminds me of another very early episode when you were living in a town called Snug. You are maybe 3 years old and you're playing outside with a bull ant, talking to it. Later you would develop a habit of singing to animals, even jelly fish.
There was no television growing up so there was a huge boredom factor. There was a lot you'd do for self amusement!

Did you ever think of becoming a naturalist?
I think that intellectually biology was really interesting to me. But a naturalist, that wasn't the way you'd find out about it—how it worked.

You really had a deep curiosity.
I had no interest in a description of things or names of species or anything like that. My mother would know all these names of plants and different flowers and I was almost rejecting. I didn't want to just know names of things. I remember really wanting to know how it all worked.

Certainly living close to nature as you did, you might ask, how do flowers develop? How do animals grow? That change through time is something you can visualize and have a sense about mechanism.
The chemistry behind it—the biochemistry—I thought, this is how you are really going to get at it. I really, really thought that and I think it was because of books I read.

Any in particular?
There was a book by [George] Gamow. He was really quite influential in molecular biology thinking. I remember reading the book and being excited by the idea that there were molecules behind life, that life was made up of molecules. It was when I was a late teenager. There was also a book by Jacob Bronowski. It was about the sciences, with really great illustrations, partially abstract pictures of instrumentation and principles behind physics and things like that. I used to read quite voraciously so those weren't the only books. But those were the ones that grabbed me for science—also the biography of Madame Curie.

I read an intriguing quote in which you said that you believed then, and you still do, that you loved science because it was a world into which you could escape. Was it an escape from something or to some place?
It wasn't like I felt I was actively escaping from something. But I was very happy in this world of the mind. So when your mind is very occupied, and you're just really interested in what you're doing, that's a great place to be. So I think it was a positive pull rather than anything that I was escaping from, except the general vicissitudes of daily life.

You had 6 siblings!
Yet we all preserved our private spaces. It was a really interesting thing when I look back on it. We're all very close to each other though we're geographically very separated. Whenever I see them we instantly reconnect.

You love animals and being outdoors and you were very comfortable in this messy, wet, chaotic world of nature.
Interesting, I never saw it as messy and chaotic.

But you've spent many, many hours in labs, which are very controlled places. Though in high school it sounds like you liked to mix things up and make explosions.
I think this happened like once! A little teenage rebellion here—like, I'll be clever. But I assure you, I was not a serial exploder. This is one daring thing me and my friends did. It felt very, very daring. And we were reproved for it.

Did you immediately feel comfortable in a chemistry lab?
Yes, I did. Right from high school, where there was a chemistry laboratory and a biology lab, I loved it.

My mother would know all these names of plants and different flowers. . . I didn't want to just know names of things. I remember really wanting to know how it all worked.

You really seemed to get it—that's something very few people do with chemistry. For most people it's quite an effort to understand what they're doing.
I was good but I wasn't brilliant at chemistry, not at all. But I really like the hand-mind connection part of it.

You had some influential teachers who helped you?
I had a very good teacher in high school who had a very good personality. When you're a teenager, that makes an enormous difference.

The field of chemistry was then and to some extent still is a male bastion. Did that register with you consciously when you decided to major in biochemistry at Melbourne University?
It did, although at this very big university there were certainly women professors in chemistry who were very distinguished in their fields. On the other hand, their numbers were low.

You described yourself to Brady as having had a "genderless mind." What do you mean by that?
I'm not quite sure.

She said that you were not, at that time, acknowledging to yourself and certainly not to others that you were different because you were a woman.
Right, this is true. I wanted to just do it. This was the subject matter I thought was interesting and it didn't matter whether I was a male or a female. I had the

strong feeling it shouldn't matter. Now I look back and think, "Well, maybe women and men do think about things differently." And that's great because this is how to solve problems—you have different minds, different ways of thinking about problems. So now I feel a little more nuanced about it. It's actually the interplay of the mind and the subject matter.

Molecular biology was on the rise when you were a biochemistry major. How would you describe the difference between molecular biology and biochemistry?
In biochemistry there's much more quantitative thinking—you find out how things work through measurement and the quantification of rates and things like that. Whereas in molecular biology there's much more an attraction to leaping . . .

To the elegant solution?
Yes, that's right and I think much of this came from physics thinking. The culture of it was very dominated by people who had been physicists, like Francis Crick and Max Delbruck—people like that. So a huge value on the elegant solution and the logic of it, which was perfect given that the information content of the genetic material was the prime focus.

Would you describe yourself as comfortable in both worlds?
I do. I love them both for different reasons.

You moved to the Medical Research Council (MRC) Laboratory of Molecular Biology at Cambridge University in 1971 to work with Fred Sanger. How would you describe Sanger's influence on you?
Very, very strong—to be at the bench all the time. I loved being there. He was somewhat laissez-faire in a good way, one that suited my temperament. He was always in the laboratory so he was always very available when you wanted to talk with him and yet he let you find your own way. I think he figured the best way to educate people was to let them explore themselves. I think that's been influential on how I mentor people. I try to give them space to do their own thinking. The idea that you are sort of slave labor to do a particular task that your advisor has thought about doesn't strike me as being the best way to get a graduate or postgraduate education. Letting the person do their own thinking is the whole key in science.

How do you cultivate independent thinking?
There's probably a certain selection for people who come to the laboratory who are ready to want to think about things. One of my students, I remember, she came and she was very clear. She said, "I want to be a student in your lab." And she said, "I don't want you telling me what to do." And I said, "You've got it!"

Sanger's was a very male-dominated lab.
Yes, it was. The whole culture very much was. There were some female scientists there but, frankly, they were not, so far as I could tell, high up in the pecking order. But we didn't talk about it. The whole culture was about science. But I loved it. I had no problem with that.

You met your future husband John Sedat there. I'm curious, there were a lot of men around in that laboratory. What drew the two of you together?
The usual chemistry.

> ***Letting the person do their own thinking is the whole key in science.***

In more ways than one!
I guess so.

It's been a real partnership, both of you passionate about science.
Right, but following different enough routes.

You did love to literally travel together. What have been some of your favorite places to visit?
Ethiopia was one of the really interesting places we went to in the early 1970s. It was John's idea to go. And I thought this was a terrific idea, too. So off we went, very adventurously. John always says I never forgave him for the 3-day bus trip across the mountains. We really were very adventurous then. I remember at one point going through the mountains on this bus. Lots of people carried rifles or arms with them all the time and on the bus suddenly everybody took their rifles off safety. We said, "What's going on?" They said, "This area is known for bandits." We were so adventurous at the time that we just took this in stride.

You were able to take off for several weeks at a time.
The work ethic was that you really worked—as we say now, 24/7. You worked day in and day out. The lights were on in the MRC laboratory till 11 o'clock or midnight every night. People were furious because they thought we were wasting electricity by leaving the lights on. People in Cambridge didn't realize that these were people who work all the time. We were a very isolated sort of culture from the surrounding Cambridge culture, which was much more, "Have a life." For us life was being in the lab.

You had good luck with mentors.
Not only luck. I've had good advice in picking good ones.

Yes, because after Cambridge you moved to Yale to work with Joseph Gall.
That was with very good input, including from John Sedat, my husband, who had known about Joe as being an excellent mentor as well as a good scientist.

It sounds like there were quite a few more women in the lab.
Yes, that was really a transformative kind of experience because suddenly it was a very different culture.

What were the salient differences?
Well, in one way it was paradoxical because at Yale, it was much more hierarchical than at the MRC laboratory in Cambridge in the sense that students and postdocs were very much in a sort of hierarchy at Yale. That wasn't the case, paradoxically enough, at this laboratory in Cambridge where any student would chat with very famous scientists at the morning tea table and things like that. But at Yale people were busier and more structured. On the other hand, suddenly in the US in the 1970s, people were much more aware that women and men should have equal opportunities so that just permeated the whole place—at least my little corner of Yale.

While you were working in the Sanger laboratory you were developing methods to sequence DNA using RNA.
Right—copying it into RNA. There were methods for sequencing RNA that had been worked out largely by Fred Sanger and some others. So that was one way of getting directly at the sequence of DNA. I had been working with this little tiny bacteriophage, ϕX174, that actually my husband John Sedat had introduced to Fred Sanger. It was a tiny single-stranded DNA, about the littlest DNA anybody knew. So John said to Fred, "Look, this would be the thing to use." And Fred thought this was a really good idea. So that was what the whole laboratory was working on in different ways.

That's what you brought to Joe Gall's lab, the knowledge of this technique?
This technique and all the other techniques that I had been so exposed to and very familiar with because there were people around me in the laboratory working on all sorts of other techniques as well. It was sort of bootstrapping your way into DNA sequences through all sorts of different avenues.

So how did you become interested in the DNA located at the tips of chromosomes?
Well, it was still unclear if we could see any DNA at all. So there had to be special tricks. Even with the very small bacteriophage ϕX174 there had to be special tricks to break it up into smaller pieces. Some of that John Sedat had devised—this was before restriction enzymes were known. We had to radiolabel the ends of DNA molecules—people had done that for λ-phage DNA. So then I thought, wouldn't it be great to look at something that wasn't viral or bacteriophage DNA but rather a regular DNA from a regular cell. Bacterial chromosomes were circular but eukaryotic chromosomes were linear. Joe Gall had found a whole lot of very small linear chromosomes, and so I thought it would be very exciting to look at the ends of these little chromosomes.

It was also at this point that you encountered a creature that would play a big role in your life.
Yes, yes—*Tetrahymena thermophila*.

> ***And then the hypothesis started coming, could they be added on to the end of chromosomes by an enzyme?***

You described it at as love at first sight.
It's a great model system but it's also a very beautiful little organism to look at through the microscope. It's a little pear shape and it swims in little spirals.

What did you see in* Tetrahymena *that led to the discovery of telomeres?
Well, there were these very uniform high–copy number little DNA molecules that you could purify out using these methods that had been worked out in Joe Gall's laboratory. So now you had this population of linear DNA molecules and it was feasible to get enough to do radiolabeling of the ends and just see what sequences could be pieced together. Even when cloning became possible it was very hard to clone the telomeres and so you had to use all these different sequencing methodologies that I learned about in Fred's laboratory. So basically I applied these methods, combinations of methods, to sequence the ends of the chromosomes. We had to make them up along the way and apply different ones depending on what you saw. Try this, try that.

Improvisation?
Very much so, because it was completely uncharted territory.

What you uncovered were these strange DNA repeats. What did you make of that?
It was just wonderfully puzzling. For a long time we had no clue what it could be. And then the hypothesis started coming, could they be added on to the end of chromosomes by an enzyme? More and more data suggested that was happening. In the 1980s, Carol Greider and I decided to look for telomerase, as we called the enzyme, in *Tetrahymena*. We knew it had lots of chromosome ends and we knew a lot of new ends were generated at a particular developmental stage in the organism. So we knew this would be a place to look for any kind of enzyme that synthesized the telomeres.

Even the idea that an enzyme was synthesizing the DNA, that was a novel leap, isn't that true?
Right. You had to propose something that nobody had ever thought of before. People knew that there were enzymes that could just stick nucleotides onto the ends of DNA but not an enzyme that could put a particular DNA sequence onto the ends of DNA without copying another DNA—that was what we were proposing. And then we hunted for it deliberately.

This enzyme was essentially creating DNA from scratch?
Well, it was copying it from RNA, which was very unusual because in molecular biology we grew up with the central dogma that in normal cells DNA should be copied into RNA and RNA should never be copied into DNA.

Now, reverse transcriptase . . .
We knew about reverse transcriptase but that had been this aberration in viruses. But it did exist and so the unusual thing then was to find out, "Okay, is this actually a reverse transcriptase that copies RNA into DNA in cells?"

But the difference between telomerase and reverse transcriptase, you proposed, was that telomerase was actually carrying its own RNA.
That's right. And it's just copying a very small portion of its own RNA. Right. But the actual active site of the protein turns out to be very close to the HIV reverse transcriptase and other known reverse transcriptases. But that's just a part of the whole story. It has this little module in it and then it has big conserved domains that bind the RNA and bind the telomeres and do other functions that we and others are still trying to figure out. It may even have roles unrelated to telomeres. All of this is still quite exciting. One thing we do know it does is synthesize DNA.

You and Carol Greider discovered telomerase late in 1984. Two years later, you discovered you were pregnant with your son Ben. You have mentioned that, by then, you had earned the ability to have a child—that you had proved yourself scientifically.
Yes, as much as I thought about it. To be honest I didn't actively think about it a whole lot. I just went along day to day.

Did having a child change your life much as a scientist? You mention the difficulty in being at 7 am meetings when Ben was a bit older.
Well that's because I was chairing at UCSF at that stage. No scientist would have a 7 o'clock meeting because we're all night owls. In the world of science, because the hours are somewhat flexible, in theory, at least, you should be able to mix having children and doing science. But because it's such a very engaging, full-time thing, in practice it becomes hard, although I've become aware now of people who've been very successful as part time scientists.

> ***You had to propose something that nobody ever thought of before.***

You describe your genderless identity as a kind of protective coloration in the male-dominated world of science. But I notice that you often remember what you were wearing on various occasions, like when you met Fred Sanger and Joe Gall. Why is this?
It has more to do with the mind. It wasn't to do with life.

Do you have a fashion sense?
I do, I do. Though I don't always use it. I'm interested in how people look. Again it's sort of aesthetic and I like to look okay. But in the world of science for many years, the idea was—it's kind of like the world of Silicon Valley is now—you dress casual.

If you could dress as you want to, what would that look like?
Well, I do try to dress a bit more. I like to be comfortable. And I do like clothes that look nice and I really like clothes that have nice lines. If I could afford it I would wear suits from Paris. I've come to realize it's possible

to be very stylish and look terrific and still be a really great scientist as well. That was a long time coming for me.

You've been photographed many times. Do you have a favorite portrait?
Hmmm. Yes, there are some that I like. There's a photographer, Micheline Pelletier, and when I got the L'Oreal UNESCO prize last year she came and took a whole lot of photographs while I was in Paris. And she came and took photographs of John and me in San Francisco. And she took some really nice ones.

What is it that you like about these photos? Do they reveal something about you?
I think they look fairly friendly and soft, some of them. I guess I like that. It's not a side of me that I've necessarily thought about. But she is a photographer and she seemed to like that aspect. It's interesting that somebody from the outside would look and see that.

A softness?
Yes, I suppose; and a pleasantness.

It was once a quiet corner of science but the whole area of telomeres and telomerase research has really exploded. How do you feel about that and what do you think are the implications of this burgeoning interest?
It deals with something fairly profound which is, why do cells stop multiplying? Why do organisms die, which is the extrapolation of that. And we're seeing connections now in people. What I like is that it takes me back to my roots in biochemistry, because now quantities are mattering again—the amounts of telomerase, the lengths of telomeres, which you can measure in people. Those turn out to have statistical relation with things like mortality. But you have to think in very different ways because it's not a nice simple mechanistic idea, where molecule A does this to molecule B. It's a complex integration of things that end up giving you a quantity—amount of telomerase, telomere length, and so forth. So it's a challenging way of thinking about things again.

The shortening of telomeres and increase in telomerase are linked with aging and cancer, respectively.
Yes, that's what's so fascinating.

There was an interesting political chapter in your life a few years ago when you were appointed to the President's Advisory Council on Bioethics. You later learned that other scientists had turned down the invitation but you accepted. Why was that?
I really thought I could offer something. I did think that national policy was important and I was intrigued by the general questions of bioethics, which were somewhat narrowly addressed by this particular council. And I thought I could really contribute to the debate, especially about stem cells because I know about cell biology and molecular biology, and I wasn't a stem cell biologist myself. So it wasn't like I had an ax to grind. I really thought I could contribute something and I'll learn something in the process.

You learned first-hand how science is affected by the broader political context. Did you become more cynical?
Not at all. I went into it very cynical. One would have to be blind not to realize that there would be a lot of political overtone to such a group. But I thought, "Look, I'm just going in as a scientist. I'm not an expert in policy, bioethics, theology—all these sorts of interesting areas that people bring to bear on these questions. But I am an expert in my particular area and I can bring honest expertise into the discussion that way." But it didn't make me more cynical.

I love that things unfold in unexpected directions, so I hope that if I took a sabbatical I wouldn't know what would be the end product.

It made you more famous.
Exactly. I was not renewed on this Council for a second term, in a sense, kicked off by the White House. What was really interesting was that huge numbers of people just got very, very upset about this because they realized it was kind of symbolic of this administration not caring about scientific evidence. I can't tell you the emails and things I was just deluged with. That to me was the opposite of cynicism. It was, this is really good! People are not just taking all of this lying down.

Any hopes for the future of science under the Obama administration?
Yes, huge hopes! They've made very clear statements that they are interested. And I'm looking at the high appointments they've made and they're clearly scientists who do take science policy very seriously.

If you had a sabbatical, how would you spend it?
Well, we did have a short one in Paris last year, and we had a wonderful time really just thinking and talking about science.

Which part of Paris?
It was the Curie Institute, a cancer-related institute that has some excellent basic research going on. I love that things unfold in unexpected directions, so I hope that I if I took a sabbatical I wouldn't know what would be the end product. This one I took, I didn't really know what the end product would be. To me that is the whole essence of a sabbatical, to have an adventure. Some people take a sabbatical to do a purpose-driven thing. I figure I can do that while I'm at the medical school. I'd like to finish the sabbatical thinking differently from the way I did when I started it. It certainly happened with the last one.

What did you come out with at the end?
It's hard to explicate. It wasn't just one individual thing. There was a huge reenergization that I felt. We'd been looking at things in telomere biology and ignoring other things—that really is what came out of it. It was "Wait a minute—there are all these stones that have been left unturned by the field and by us, and we need to be looking at things in different ways for telomeres. We need to try to think about them as very, very dynamic entities."

What do you like to do to relax, if you do relax? Do you read novels?
I'm reading Simon Winchester's book about Joseph Needham. And I like spy stories.

Which in particular?
I've enjoyed the John LeCarre spy stories. They're very gloomy.

You like gloomy?
No, but for some reason I like that sort of gloomy world of fiction. And his novels are very morally ambiguous. I guess I like that subtlety about them. I'm sure I wouldn't agree with his philosophies half the time. But he raises moral ambiguities so they are really intriguing.

When do you find time to read?
Coming back from the east coast on airplane trips—that's the time I really read because I'm too exhausted to do anything. Lots of my friends say they get lots of work done flying back from the east coast and I can't believe them for a moment. I'm just way too exhausted.

What's your favorite time of the day?
What an interesting question! Lunch time.

Why?
You take a break and you do something interesting at lunch time. You talk with people.

Finally, what would be your advice to a young woman starting out in biochemistry or the life sciences today?
Well, I guess the usual things, like "Go for it." And don't be afraid to ask people for help—and then feel free to ignore it! I think that was what I didn't do well. I was not good at getting helpful advice. I think I was too proud and I had all the answers.

You had quite a few good ones.
I'm sure I could have done better.

Reference

1. Brady C. Elizabeth Blackburn and the story of telomeres: deciphering the ends of DNA. Cambridge (MA): The MIT Press; 2007. 424 p.

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